Neonatal epilepsy

Treatable neonatal epilepsy

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Perspective on the paper by Bok *et al* (***see page 687***)

Treatable metabolic causes of early onset epilepsy (in the first few months of life) are uncommon but it is important to diagnose them because delay in specific treatment commonly results in poor neurological and cognitive outcome. Indeed, some of these epilepsies are fatal if left untreated. The disorders are listed in table 1 and are divided into vitamin-responsive and other metabolic epilepsies.

We are not going to discuss all of these disorders, but will confine ourselves to those presenting at or very close to birth. The investigation and treatment of the other epilepsies are summarised in table 2.

PYRIDOXINE-DEPENDENT EPILEPSY

Typical neonatal onset pyridoxine-dependent epilepsy (PDE) presents in the first few days of life with multiple seizure types which are intractable to anticonvulsant drug treatment. Experienced mothers may also recognise seizures in utero from about 20 weeks of gestation. Approximately one third of infants with PDE will also have features of a neonatal encephalopathy (hyperalertness, irritability and a stimular sensitive startle) which can be accompanied by systemic features. Neuroimaging may show structural brain abnormalities, hydrocephalus or haemorrhage. EEG is abnormal but has no diagnostic features.[1] The seizures and EEG abnormalities respond promptly (within minutes) to 100 mg of intravenous pyridoxine. However, in about 20% of infants with pyridoxine-dependent epilepsy the first dose of pyridoxine can also cause cerebral depression, which is more likely if the infant is receiving anticonvulsant drugs. Children with PDE require life-long treatment with pyridoxine at a dose of ~15 mg/kg/day up to 500 mg/day. With prompt treatment prognosis is generally good, although there may be later learning difficulties, particularly with language. If treatment is delayed by months or years, children develop severe learning difficulties, four limb motor disorder and sensory disturbances.

Table 1 Treatable metabolic causes of early onset epilepsy

Vitamin-responsive epilepsies
Pyridoxine-dependent epilepsy
Pyridox(am)ine phosphate oxidase deficiency (pyridoxal phosphate-responsive epilepsy)
Folinic acid-responsive seizures
Biotinidase deficiency
Other metabolic epilepsies
Glucose transporter 1 deficiency
Serine deficiency syndromes
Creatine deficiency syndromes
Untreated phenylketonuria

The major cause of PDE has been recently identified[2] as being due to mutations in the *ALDH 7A1* gene which encodes a central nervous system α-aminoadipic semialdehyde dehydrogenase. This results in accumulation of α-aminoadipic semialdehyde (α-AASA). α-AASA is in reversible equilibrium with piperideine-6-carboxylate which can condense with pyridoxal phosphate and inactivate its cofactor activity. The build-up of α-AASA and its spill-over into plasma and urine make it a specific and sensitive marker of PDE caused by α-aminoadipic semialdehyde dehydrogenase deficiency.[2] Another metabolite more proximal in this lysine degradation pathway is pipecolic acid, and this is also raised in PDE but is less specific and sensitive than α-AASA.[3] Both markers remain raised after treatment with pyridoxine. This is demonstrated in this issue of *ADC* by Bok *et al* who have shown that all patients in the Netherlands with clinically definite PDE (according to Baxter's criteria[4]) and six of eight patients with clinically probable or possible PDE had raised urinary and plasma α-AASA concentrations (one patient was not tested and one was negative). In these patients plasma, but not urinary, concentrations of pipecolic acid were also raised. Bok *et al* also calculate that PDE caused by α-aminoadipic semialdehyde dehydrogenase deficiency has a birth incidence in the Netherlands of at least 1:276 000.

PYRIDOX(AM)INE PHOSPHATE OXIDASE DEFICIENCY

Pyridox(am)ine phosphate oxidase (PNPO) deficiency presents as foetal distress in late pregnancy. Seizures start in the first few days of life after birth and are intractable to anticonvulsant drugs. EEG is abnormal with no normal background activity and bursts of spike-wave discharges. Neuroimaging is normal at the onset. There is no response to intravenous pyridoxine. However, there is a prompt and lasting response to oral pyridoxal phosphate (hence the alternative name of pyridoxal phosphate-responsive seizures) given at a dose of 10 mg/kg. Like PDE, treatment of PNPO deficiency with pyridoxal phosphate can cause transient cerebral depression. Again treatment is life-long, requiring pyridoxal phosphate at a dose of 30–50 mg/kg/day. With prompt treatment the prognosis is generally good. However, if left untreated, most cases of PNPO deficiency are fatal in the first year, and rare survivors have severe neurological handicap and profound brain atrophy.[5 6]

Some biochemical markers of PNPO deficiency are evident in cerebrospinal fluid and plasma.[5] Because vitamin B_6 crosses from cerebrospinal fluid into neural cells as phosphorylated esters of pyridoxine and pyridoxamine as well as pyridoxal, PNPO is necessary to convert the pyridoxine phosphate and pyridoxamine phosphate to the active cofactor pyridoxal phosphate. Pyridoxal phosphate is the cofactor for over 100 enzymes involved in amino acid and amine metabolism, three of which are L-aromatic amino acid decarboxylase (AAAD), the glycine cleavage system and threonine dehydratase. Dysfunction of the latter two enzymes results in a mild increase in the concentrations of glycine and threonine, respectively, in both plasma and cerebrospinal fluid. AAAD dysfunction causes a reduction in cerebrospinal fluid concentrations of homovanillic acid (the stable acidic metabolite of dopamine) and 5-hydroxyindoleacetic acid (the stable acidic metabolite of serotonin) and an increased concentration of 3-methoxytyrosine. These biochemical abnormalities are not present in all patients.[6] However, if they are present, they reverse with treatment.

The birth incidence of PNPO deficiency is not known.

FOLINIC ACID-RESPONSIVE SEIZURES

Folinic acid responsive seizures is the least well recognised cause of vitamin-responsive neonatal epilepsy.[7 8] Infants present in the first few days of life with multiple seizure types which are intractable to anticonvulsant drugs. They may also have features of a neonatal encephalopathy. EEG shows abnormal background activity with multifocal spike-wave complexes but no diagnostic features. Neuroimaging is normal. There can sometimes be a transient

Table 2 Investigation and treatment of metabolic causes of early onset epilepsy

Disorder	Investigation	Treatment
Biotinidase deficiency	Trial biotin 5 mg twice daily Plasma biotinidase activity	Biotin 5–10 mg twice daily
GLUT1 deficiency	CSF glucose <2.2 mM, CSF/plasma glucose <0.5 Red cell glucose transport Mutation analysis of *SLC2A1* gene	Ketogenic diet
Serine deficiencies	Reduced fasting plasma serine (and variably glycine) Reduced CSF serine and glycine Fibroblast 3-phosphoglycerate dehydrogenase or phosphoserine aminotransferase activity Mutation analysis of *PHGDH* and *PSAT1* genes	Serine 200–600 mg/kg/day (glycine 200–300 mg/kg/day)
Creatine deficiencies	Urine creatine/creatinine ratios, urinary guanidinoacetate/creatinine ratio Reduced CSF creatine Reduced cerebral creatine plus creatinine (^{1}H-MRS) Fibroblast guanidinoacetate methyltransferase activity Mutation analysis of *GAMT*, *AGAT* and *SLC6A8* genes	GAMT deficiency: creatine 500–2000 mg/kg/day, arginine-restricted diet with ornithine supplementation (100 mg/kg/day).
Untreated PKU	Plasma phenylalanine Mutation analysis of *PAH* gene	Phenylalanine-restricted diet

AGAT, L-arginine:glycine amidinotransferase; CSF, cerebrospinal fluid; GAMT, guanidinoacetate methyltransferase; GLUT1, glucose transporter 1; ^{1}H-MRS, proton magnetic resonance spectroscopy.

response to pyridoxine. The seizures promptly respond to folinic acid at a dose of 2.5–5 mg twice daily. However, seizures can recur later, sometimes responding to increases in folinic acid alone (up to 8 mg/kg/day) and sometimes also requiring anticonvulsant drug therapy. If left untreated, folinic acid-responsive seizures is a fatal disorder. Even with treatment and control of the epilepsy, there is appreciable mortality and survivors have global learning difficulties.

Folinic acid-responsive seizures does have a biochemical marker in cerebrospinal fluid, but its nature is unknown. It is detected by high performance liquid chromatography with electrochemical detection under the conditions required to measure homovanillic acid and 5-hydroxyindoleacetic acid. This unknown compound is not normally present in cerebrospinal fluid and decreases once treatment with folinic acid has been initiated.

The birth incidence of folinic acid-responsive seizures is not known.

APPROACH TO DIAGNOSIS

There are two possible approaches to diagnosing these treatable neonatal epilepsies. The first is to give the relevant vitamins and observe the response. In our view, this is the correct and also the easiest approach. The second method is to investigate the biochemical markers for each condition. This will require the help of a specialised (often highly specialised) metabolic laboratory. Because this approach will take time and typical biochemical abnormalities will not be present in all cases,[6] we advise treatment before starting such investigations.

APPROACH TO NEONATAL EPILEPSY

Once precipitating conditions such as infection, hypoglycaemia or electrolyte, calcium and magnesium disturbance have been excluded or corrected, we believe the next line of investigation and treatment in neonatal epilepsy is to initiate a vitamin trial. We suggest giving two doses of pyridoxal phosphate (10 mg/kg/dose) 2 h apart, and, if the epilepsy persists, two doses of folinic acid (5 mg) 6 h apart. EEG monitoring is helpful but not mandatory. If there is no response to the vitamins, anticonvulsant therapy should be introduced and further investigations into the cause of the epilepsy carried out.

There are three lines of reasoning behind this view as follows.

Firstly, it has recently become clear that there are physiological reasons why anticonvulsant drugs which act as GABA-agonists might not be as effective in newborns as in older children and adults. These anticonvulsant drugs include phenobarbitone and benzodiazepines. There is also increasing evidence from animal studies that phenobarbitone, phenytoin and the benzodiazepines are toxic to the newborn brain, causing increased neural apoptosis. These findings suggest that standard anticonvulsant treatment of neonatal seizures may not be as effective or as safe as previously believed.[9 10]

Secondly, there is no biochemical or chemical reason to believe that pyridoxal phosphate will not be as effective as pyridoxine in the treatment of PDE. PDE can be distinguished from PNPO deficiency later by measuring urinary α-AASA excretion, and a firm diagnosis made by mutation analysis of DNA. It is also important to remember that α-aminoadipic semialdehyde dehydrogenase deficiency is not the only cause of PDE, and a small proportion of cases will be missed by biochemical analysis unless pyridoxal phosphate is tried. If pyridoxal phosphate is not easily available, pyridoxine should be given as first line therapy. It must, however, not be forgotten that unsuccessful treatment with pyridoxine does not exclude PNPO deficiency.

Thirdly, delayed diagnosis of these conditions can cause severe neurological handicap and early death.

Arch Dis Child 2007;**92**:659–661.
doi: 10.1136/adc.2007.116913

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Competing interests: None.

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Children's medicines

''Bonne Année'', ''Gutes Neues Jahr''? Will 2007 be a ''Happy New Year'' for children's medicines in Europe?

T Stephenson

New European legislation has the potential to have an enormous impact on how paediatric medicines are studied and used

New European Union (EU) paediatric regulations to encourage more research on children's medicines became law on 26 January 2007.[1] The main proposals are as follows. First, there will be incentives to encourage the pharmaceutical industry to test products for use in children. Secondly, the European Agency for the Evaluation of Medicinal Products (EMEA) will host an expert paediatric committee to oversee and assess paediatric investigation plans for developing medicines for children. Thirdly, a European clinical trials network will be set up to foster collaboration on paediatric studies throughout the EU. Fourthly, medicines licensed for paediatric use should be sold with a special label indicating that fact.

This legislation has the potential to have an enormous impact on how paediatric medicines, both old and new, are studied and used. Is this good news for Europe's 140 million children?

THE DRIVERS FOR THE NEW EUROPEAN LEGISLATION

Evidence-based prescribing for children is compromised by lack of sufficient data on many drugs.[2–4] Although there is an elaborate system for testing drugs before they are used in adults, many drugs given to children have not been tested in this population at all, even though children can react differently to drugs.[5] Moreover, it is often financially unrewarding to conduct research on medicines for children because the children's market is smaller than that of adults.

If evidence for the safety, efficacy and acceptable risk/benefit of a drug exists, then that drug can be licensed for use as a medicine with indications, doses and side-effect warnings. However, prescribing can also be unlicensed (eg, the medicine is given as a liquid whereas the licence is for a tablet) or outside the terms of the licence (off-label; eg, a different dose for a different age group). Half of prescriptions for children and 90% of prescriptions for neonates are for drugs which have not been licensed for that use.[6–8] Every day, paediatricians face the dilemma of whether it is more unethical to prescribe a drug that has not been tested or to deny treatment to a sick child.

Whether a medicine is beneficial and safe in children is best determined by studying it in children. Where the market is large (eg, antibiotics) or the price is high (eg, surfactant), companies do conduct well planned studies in children and secure licences, suggesting that the industry can overcome ethical problems[9 10] and litigation risks if the price is right.[11] However, because of the cost of developing drugs[12] and the small market in children, recouping research costs before the patent expires is uncertain.

THE US EXPERIENCE

The ''paediatric exclusivity'' provision in the Food and Drug Administration Modernisation Act 1997 provided an incentive (6 months added to market exclusivity or patent protection on the active drug) for companies who performed clinical studies in children.[13] The incentive was granted irrespective of whether the results demonstrated safety and efficacy in children or, equally importantly, suggested the drug should not be used in children.

As of 2004, the data generated had led to revised labelling (ie, new dose, route or indication) for 63 medicines and 661 studies had been requested. The incentives have therefore been successful in the US in stimulating paediatric studies and ensuring that more paediatric data are available to prescribers, although not always for the most important medicines.[14 15] The largest category considered for paediatric studies was cardiovascular drugs (n = 36), including 22 anti-hypertensives, suggesting choice was not due to paediatric need.[15] The financial gains were higher for ''blockbuster'' drugs since the 6 months' extension of patent protection applied to all formulations of the drug type, whether appropriate for paediatric use or not. The current US regulations have a ''sunset'' clause in 2007 unless renewed by Congress.

The US measures brought little benefit to European children. International companies appear unwilling to voluntarily submit US data to support authorisation for children in the EU, presumably because of the lack of financial incentives in Europe. Progress in Europe appeared unlikely without legislation.

THE NEW EUROPEAN LEGISLATION

The key measures included in the new European paediatric regulations cover both older and newer medicines.

For newer medicines

All applications for a marketing authorisation for a new medicine, including orphan medicines, must contain the results of all studies and information required in a previously agreed paediatric investigation plan (PIP). The PIP will contain a full proposal of all the studies (and their timings) necessary to support the paediatric use of an individual product and will cover all paediatric age groups and all necessary age-appropriate formulations. This is the default position of the regulation.

There is a system of waivers for medicines unlikely to benefit children so that children are not studied unnecessarily. There is also a system of deferrals of the requirement to study the childhood population to ensure that medicines are tested in children only when it is safe to do so and to prevent the requirements delaying the authorisation of medicines for adults. In this case, the paediatric data will be provided after the initial marketing authorisation has been granted. But unless a deferral or a waiver has been granted, paediatric data must be provided in all applications for the authorisation of new medicinal products. This applies from 26 July 2008.

The requirement also applies to applications to add a new indication, new formulation or new route of