

Childhood epilepsy: the biochemical epilepsies

Dr Colin D Ferrie

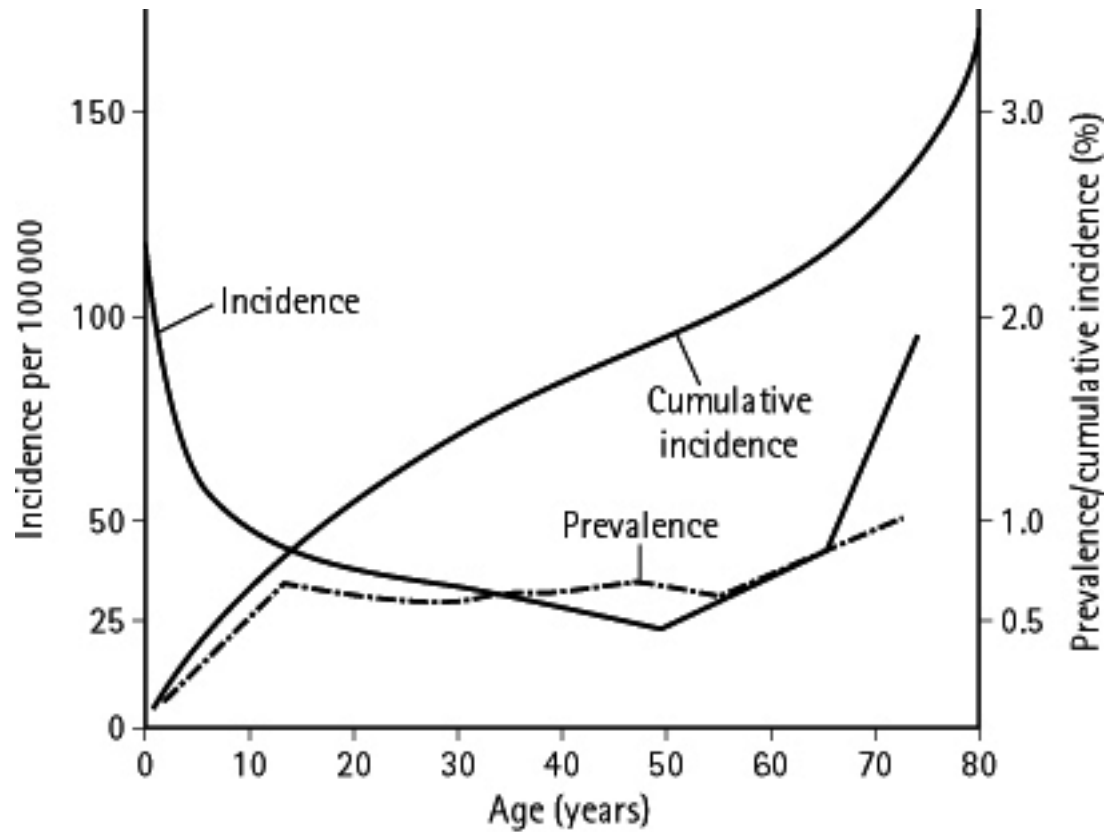
Consultant Paediatric Neurologist

Leeds General Infirmary

Definitions

- **Epileptic Seizure**
 - Manifestation(s) of epileptic (excessive and/or hypersynchronous), usually self-limited activity of neurones in the brain
- **Epilepsy**
 - A chronic neurological condition characterised by recurrent epileptic seizures
- **Epilepsy Syndrome**
 - A complex of signs and symptoms which define a unique epilepsy condition
- **Epileptic Disease**
 - A pathologic condition with a single, specific, well-defined aetiology

Epidemiology



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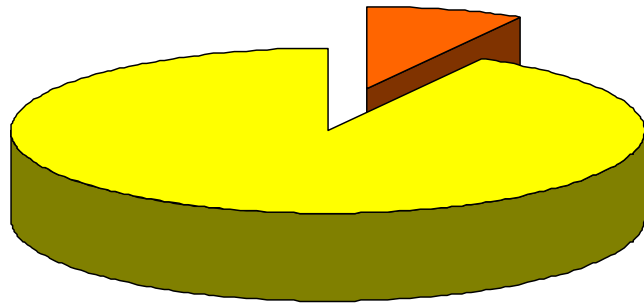
Classification: The ILAE Diagnostic Scheme

- Axis 1 – A Glossary of terms
- Axis 2 – Epileptic Seizures
- Axis 3 – Epilepsies and Epileptic Syndromes
- Axis 4 – Aetiology
- Axis 5 – Functional Consequences

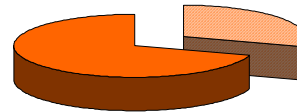
What Causes Epilepsy in Children?

- Ion channel disorders
- Malformations of cortical development
- Neurocutaneous disorders
- Chromosomal and monogenic mendelian disorders
- Pre, peri and postnatal destructive processes (ischaemic, anoxic, infections, trauma, etc)
- Tumours
- Inherited metabolic disorders (including the progressive myoclonic epilepsies) - 'the biochemical epilepsies'

These are all very rare!



Epilepsy



Inborn error of metabolism

'Biochemical' seizure disorders with neonatal onset

Reasons to suspect

- Family history
 - Most are recessive conditions
- In-utero hiccups
 - Some cause seizures in-utero
- Myoclonic seizures
 - Myoclonic seizures occur in many types of epilepsy, but are particularly characteristic of 'biochemical seizure disorders'
- Intractable seizures
 - Most do not respond at all or at all well to conventional AEDs
- Associated encephalopathy
 - Beware HIE
- Dysmorphic features
 - E.g. Zellweger's syndrome
- Burst-suppression EEG

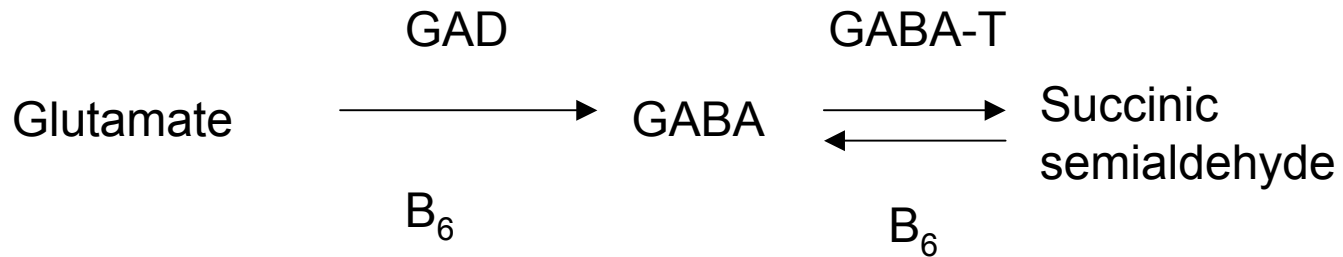
'Biochemical' seizure disorders with neonatal onset

- Vitamin dependent seizures
 - Pyridoxine dependency
 - Pyridoxal phosphate dependency
 - Folinic acid responsive seizures
- Amino acid disorders, including neurotransmitter abnormalities
 - GABA transaminase deficiency
 - Non-ketotic hyperglycinaemia (glycine encephalopathy)
 - Sulfite oxidase deficiency & molybdenum cofactor deficiency
- Urea cycle disorders
- Organicacidurias
- Aminoacidurias
- Mitochondrial disorders
- Peroxisomal disorders

Pyridoxine dependent seizures

- Classically begins in very early neonatal period with drug resistant convulsive seizures \pm encephalopathy
- In-utero onset well recognised
- Onset may be up to 3 years of age with a variable seizure phenotype
- Need to distinguish pyridoxine responsive and pyridoxine dependent seizures
- Outcome highly variable

Pyridoxine dependent seizures



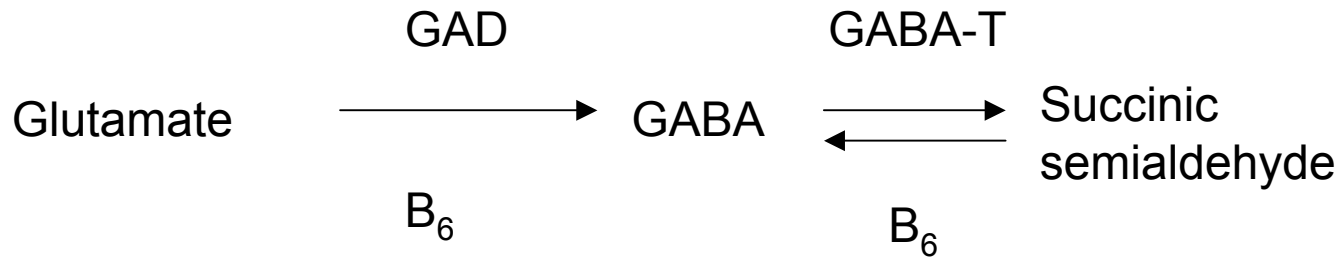
Mutations in the ALDH7A1 gene (5q31) which codes for antiquitin is the cause of pyridoxine dependent seizures.

Abolition of antiquitin activity eventually leads to inactivation of pyridoxal 5'-P

Diagnosis can now be established by urinary measurement of α -AASA

Prenatal diagnosis can be made by ALDH7A1 gene analysis

Pyridoxal 5' phosphate dependent seizures



Pyridoxal 5'-P is the active form of pyridoxine and is formed from pyridoxine by the activity of the enzyme PNPO

Deficiency of PNPO causes pyridoxal phosphate dependent seizures

The diagnosis is aided by CSF neurotransmitter analysis [aromatic L-amino acid decarboxylase (AADC) deficiency]

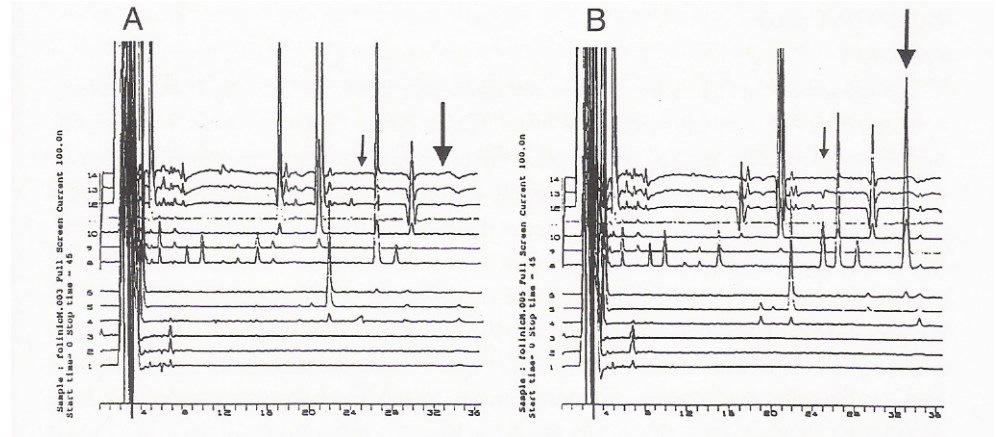
Folinic acid responsive seizures

Clinical Features:

- Intractable neonatal seizures
- May be associated encephalopathy

Diagnosis:

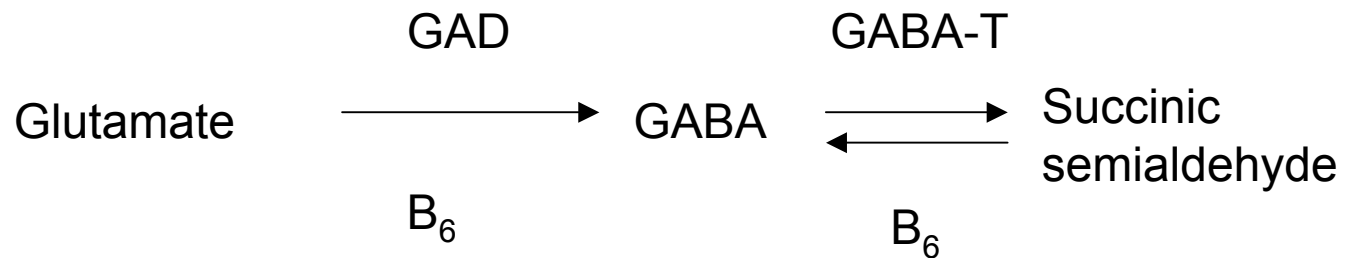
- CSF chromatography
- Trial of folinic acid



Treatment:

- Oral folinic acid

GABA transaminase deficiency



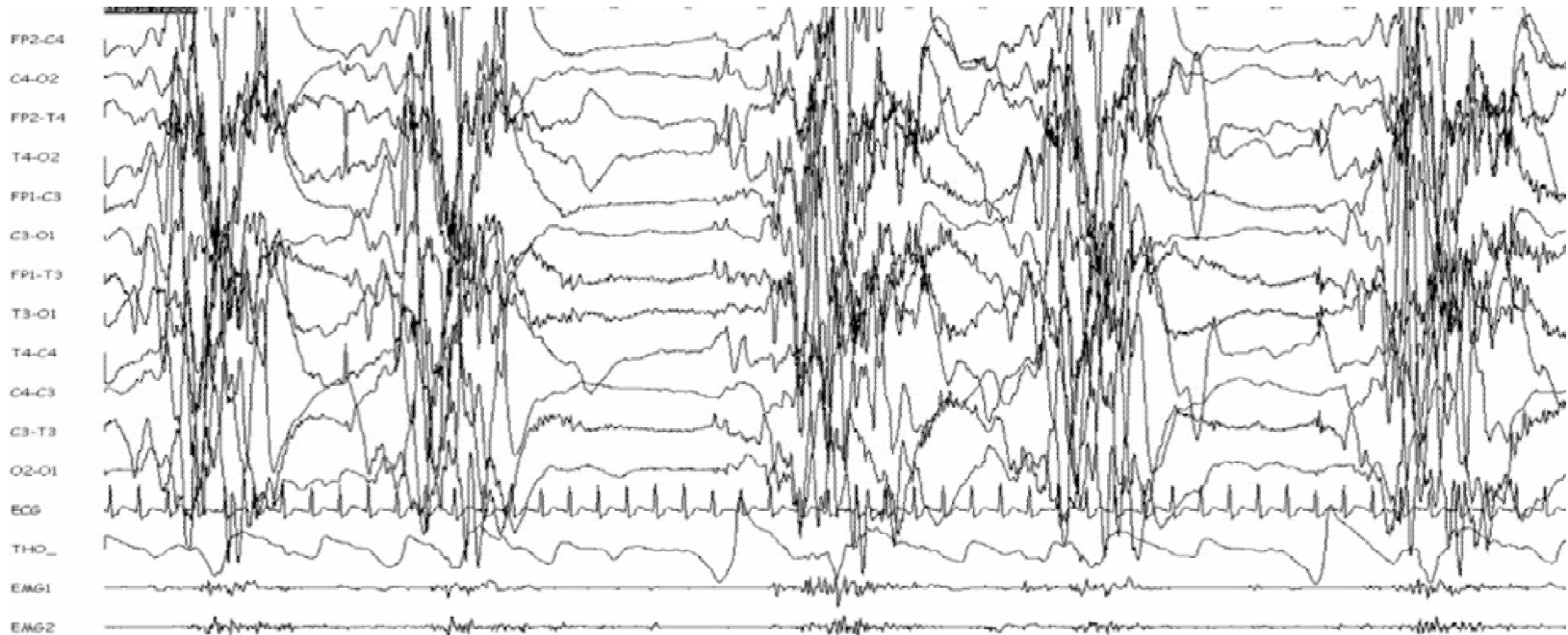
GABA transaminase (GABA-T) deficiency is exceptionally rare

Seizures are associated with severe retardation and increased somatic growth (including megalencephaly)

GABA and various metabolites are increased in plasma and other body fluids

Glycine encephalopathy

- Characteristically leads to early myoclonic encephalopathy



Caused by disorders of the glycine cleavage system, leading to accumulation of glycine in various body fluids

Prenatal diagnosis is possible enzymatically or genetically

Sulfite oxidase deficiency & molybdenum cofactor deficiency (MCD)

- Sulfite oxidase deficiency can be a single enzyme deficiency or part of deficiency of the molybdenum cofactor-containing enzymes
- In either case:
 - Autosomal recessive
 - Severe & irreversible brain damage from birth resembling HIE
 - Intractable neonatal seizures



Diagnosis:

- Sulfituria by dipstix
- Accumulation of thiosulfate, S-sulfocysteine and taurine in plasma and urine (chromatography)
- MCD is also associated with hypouricaemia and xanthiuria
- Enzyme activities on cultured fibroblasts

‘Biochemical’ seizure disorders with onset in infancy, childhood and adolescence

- Biotinidase deficiency
- Glut-1 deficiency
- Serine synthesis disorders
- Creatine synthesis disorders
- Some of the progressive myoclonic epilepsies
 - Myoclonic epilepsy with ragged red fibres (MERRF)
 - Ceroid lipofuscinoses
 - Sialidoses

Biotinidase deficiency

- Biotin is a vitamin essential for the function of four carboxylase enzymes involved in diverse areas of intermediary metabolism
- Biotinidase is an enzyme responsible for recycling of biotin

Clinical Features:

- Autosomal recessive
- Alopecia & dermatitis
- Fatigue, hypotonia & lethargy → Coma
- Ataxia
- Seizures (esp myoclonic)

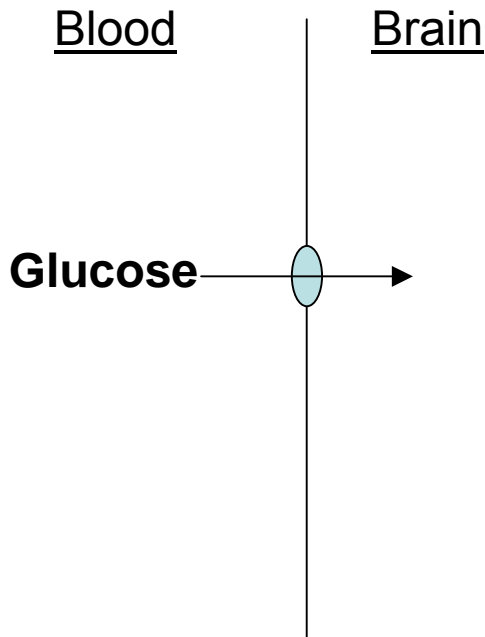
Diagnosis:

- Urinary organic acids
- Serum biotinidase

Treatment:

- Oral biotin

Glut-1 Deficiency



 = glucose transporter

Clinical features:

- Refractory seizures (GTCS; absence; others)
- Apnoeas
- Abnormal eye movements
- Developmental delay & acquired microcephaly

Diagnosis:

- Low $[\text{CSF}]_{\text{glucose}} : [\text{blood}]_{\text{glucose}}$
- Glut-1 transporter functional assay in erythrocytes
- GLUT-1 mutational analysis

Treatment:

- Ketogenic diet

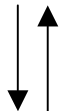
Serine Biosynthesis Disorders

Glycolysis



*3-phosphoglycerate
dehydrogenase*

Serine



Glycine

Clinical features:

- Congenital microcephaly & severe retardation
- Seizures
- Polyneuropathy

Diagnosis:

Low fasting CSF [serine]

Treatment:

- Oral serine supplementation

The biochemical epilepsies: summary 1

	Biochemical test	Biochemical treatment
Pyridoxine dependent seizures	±	√
Pyridoxal P dependent seizures	±	√
Folinic acid responsive seizures	±	√
GABA transaminase deficiency	√	X
Non-ketotic hyperglycinaemia	√	X
Sulfite oxidase & molybdenum cofactor deficiencies	√	X

The biochemical epilepsies: summary 2

	Biochemical test	Biochemical treatment
Biotinidase deficiency	√	√
Glut – 1 deficiency	√	√
Serine synthesis disorders	√	√
Creatine synthesis disorders	√	√
Progressive myoclonic epilepsies	±	X