Metabolic disease presenting as epilepsy

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Overview

1. Age-dependent approach:

- neonates/infancy
- later childhood
- adolescence

2. Emphasis on treatable disorders and important diagnoses

- Vitamin B6
- GLUT1

Definitions

- Inborn errors of metabolism
- Present with epilepsy as a major feature in infancy

- Rare
- Important to recognise
- Many currently treatable
- Genetic basis for majority of IEM now elucidated
- Implications for genetic/prenatal counselling

IEM and Age of Epilepsy Presentation

NEONATAL/EARLY INFANCY	LATE INFANCY/EARLY CHILDHOOD	LATE CHILDHOOD/EARLY ADULTHOOD
PDE, PNPO	Milder PDE/PNPO	CoQ10 deficiency
CDG	CDG	Lafora Body/UVL
Congenital NCL	Infantile/late infantile NCL	Juvenile NCL
Biotinidase deficiency	Mitochondrial including Alpers	MERFF
GLUT1	Gangliosidosis/sialidosis	MELAS
NKH	Creatine synthesis defects	*POLG*-related disorders
Serine biosynthesis disorders		Late-onset GM2 gangliosidosis
MoCoF and SOX deficiency		Gaucher type III
Peroxisomal disorders		Peroxisomal disorcers
Menkes		NPC

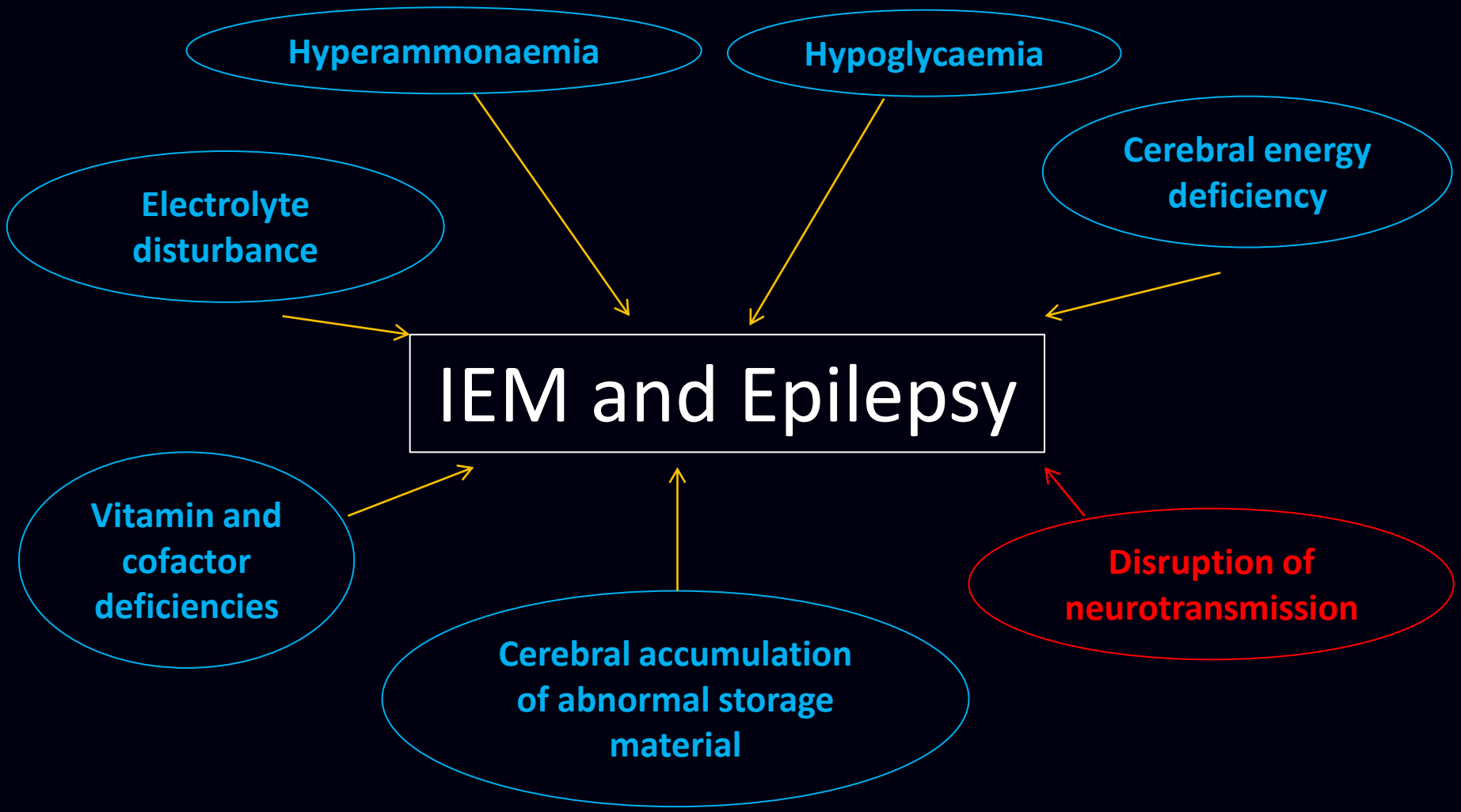
Adapted from Rahman et al Dev Med Child Neurol Sept 2012 epub ahead of print

Clinical Clues to IEM causing epilepsy

- Early onset seizures – wide differential
- Parental consanguinity, affected sibling
- Abnormal fetal movements
- Seizures related to metabolic stress
- Facial dysmorphia, hair, skin
- Ophthalmological assessment
- Multisystemic involvement
- EEG
- MRI/MRS

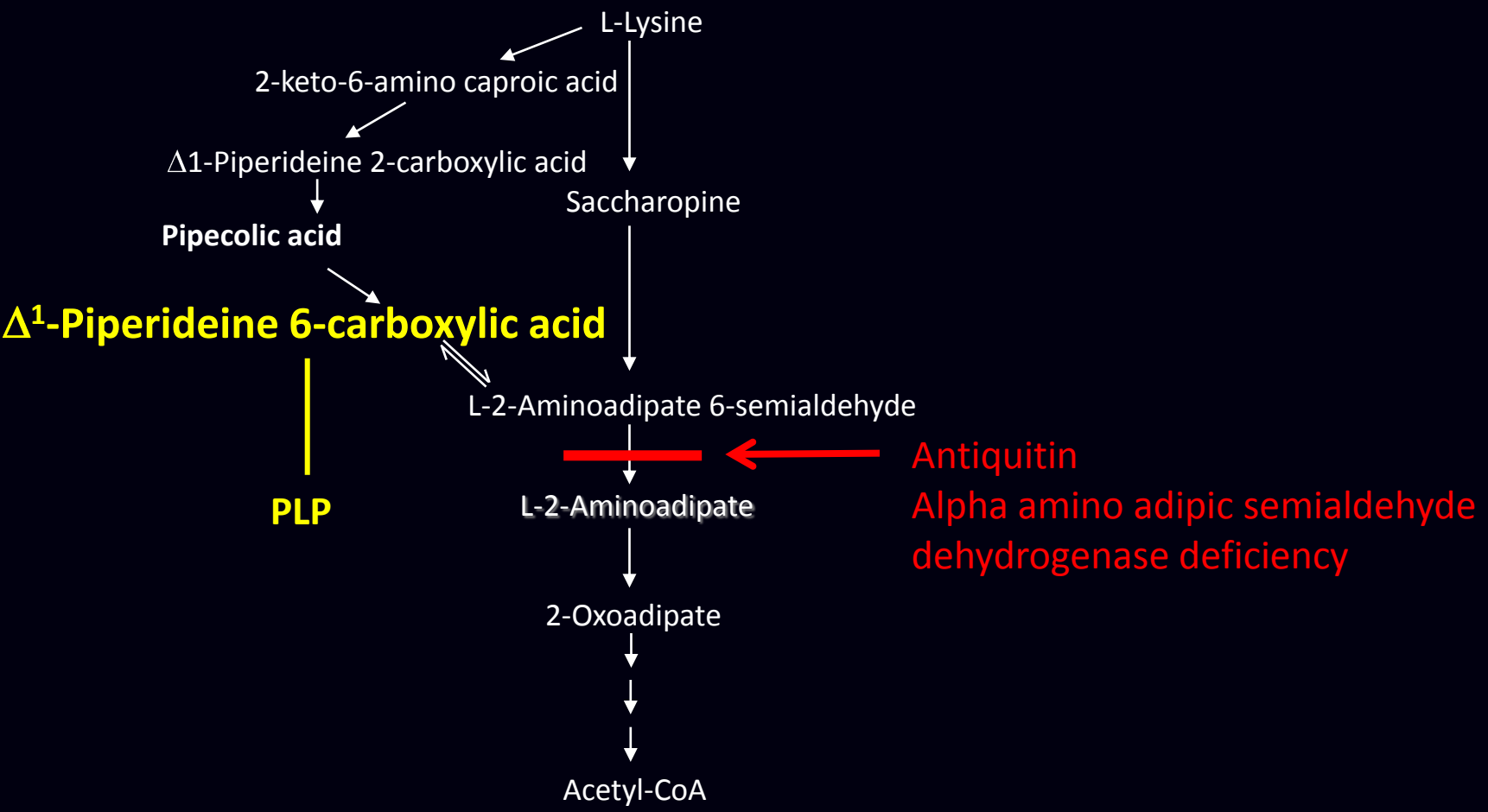
- Seizure type?

IEM in Infantile Epilepsy

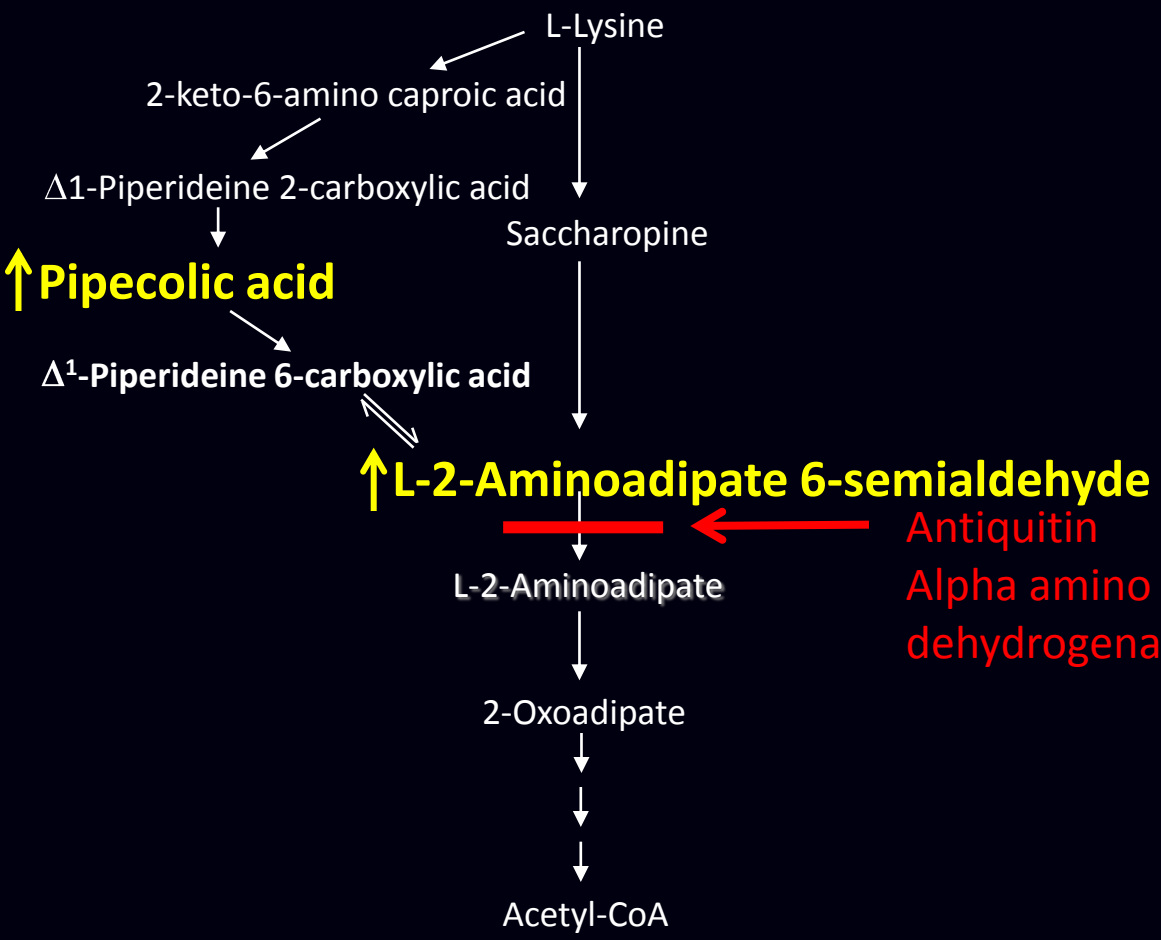


- Floppy at birth
- Numerous seizure types – myoclonic, multifocal
- Abnormal eye movements, grimacing, irritable
- Failure of multiple AED
- Responded to trial of pyridoxine

Pyridoxine-dependent seizures



Pyridoxine-dependent seizures



Diagnosis of pyridoxine-dependent epilepsy

- Trial of pyridoxine with EEG monitoring then oral treatment
- Urine/plasma/CSF αAASA
- CSF/plasma Amino acids
- CSF Pipecolic acid
  Pyridoxal phosphate
  HVA/HIAA
  3-methoxytyrosine
- Genetics

Folinic Acid Responsive Seizures

Folinic Acid–Responsive Seizures Are Identical to Pyridoxine-Dependent Epilepsy

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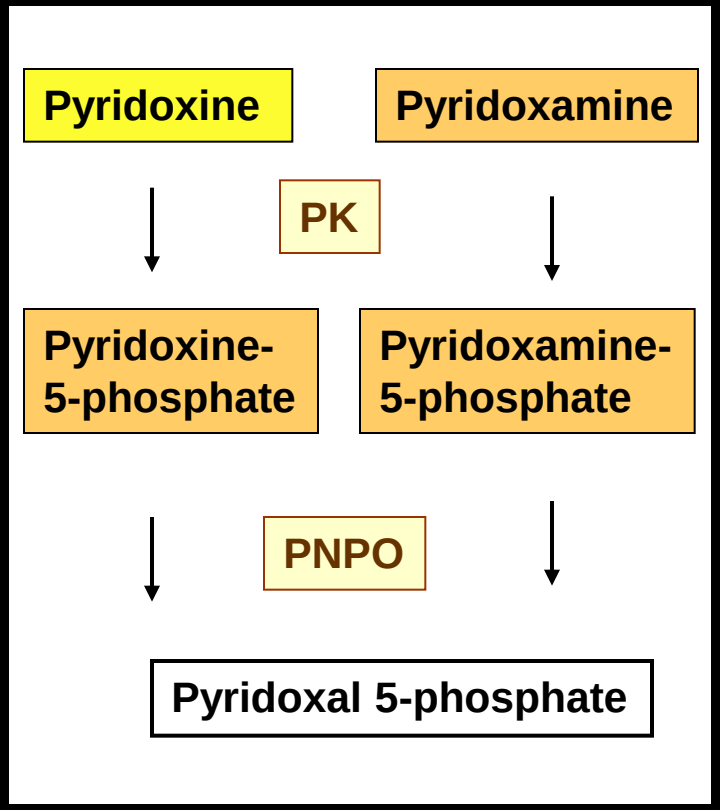
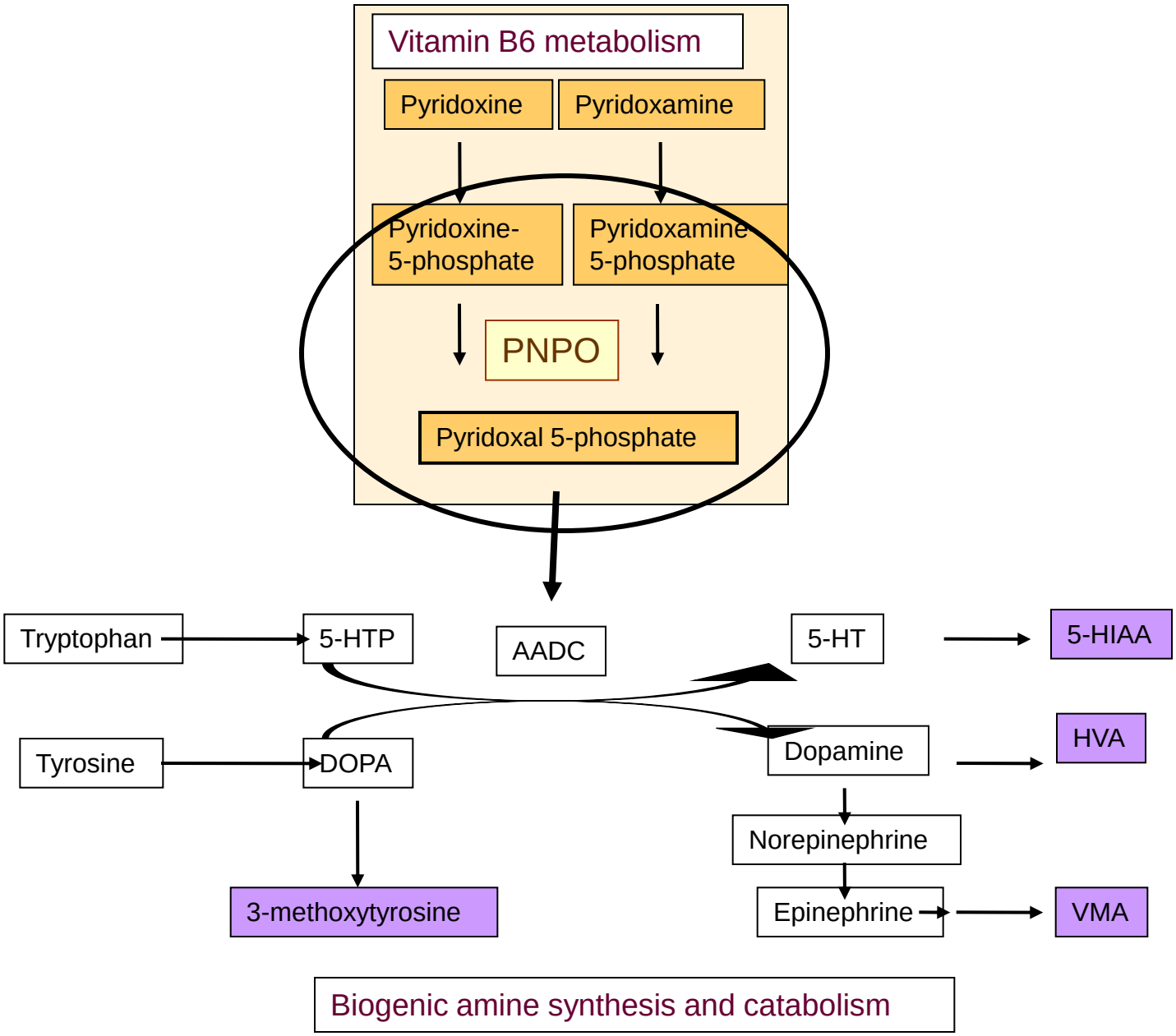
- Originally thought to be a distinct clinical entity
- Characteristic peak on CSF HPLC
- Some patients responded to pyridoxine
- AASA elevation, mutations in antiquitin
- 2 disorders biochemically and genetically identical

Vitamin B6 Metabolism

- 3 dietary forms of water-soluble vitamin B6:
  - pyridoxine (vegetables)
  - pyridoxamine (red meat)
  - pyridoxal phosphate (all converted to this active form)





Biogenic amine synthesis and catabolism

PNPO deficiency

- Only described in a few families
- FH – miscarriages, infertility
- Often premature
- Severe neonatal seizures
- Multifocal, myoclonic, tonic
- EEG – burst suppression pattern

PNPO deficiency

- Reduced PLP metabolites in CSF
- Reduced HVA/HIAA
- Mutational analysis of *PNPO*

- Responsive to pyridoxal phosphate
- 10-30mg/kg/d
- Monitor LFTs

Treatment points (1)

- Life-long supplementation in pharmacological doses
- No clear-cut dosing recommendations
- Pyridoxine
  - 15-30mg/kg/d up to a maximum of 200 mg/day in neonate, 500mg/day in adults
  - If breakthrough seizures with febrile illnesses, prophylactically double the dose for first three days
  - Association with peripheral neuropathy, may be reversible

Treatment points (2)

- Pyridoxal phosphate
  - For PNPO and other B6-responsive seizures
  - 30- 40 mg/kg/d in at least 4 doses
  - Crushed tablets can be bitter
  - some patients with proven PNPO get symptoms 3 - 4 hours, so have to go up 100 mg/kg/d in 8 doses
  - monitor LFT's and liver size in high dose
  - Avoid - L-dopa, carbidopa, isoniazid, penicillamine
  - Less easily available, only licensed in Japan

Treatment points (3)

- Folinic acid add-on may be helpful
  - 3-5mg/kg/day neonates, 10-30mg/day older patients
- Lysine restricted diet, a future treatment?
- Prophylactic pre-and post-natal treatment
  - 25% recurrence risk for PDE
  - Possibly improves outcome

Glucose Transporter Deficiency (de Vivo Syndrome / GLUT1 Deficiency Syndrome)

- Disorder of brain energy metabolism
- Impaired GLUT1-mediated glucose transport into the brain

Glucose Transporter Deficiency (de Vivo Syndrome / GLUT1 Deficiency Syndrome)

- SCL2A1 gene (Seidner, Nat Genet 98, Wang Ann Neurol 2005)
- Small gene on chromosome 1, highly conserved protein
- De novo heterozygote mutations
- Loss of function of one of the alleles
- What is new? Expanding spectrum
  - Klepper, DMCN 2007; Leen, Brain 2010)
- Autosomal dominant – familial transmission

GLUT1 DS phenotypes

- Now recognise three phenotypes
  - Classical (84%)
    - Early-onset (<2yrs)
    - Late-onset (18%)
  - Non-classical with mental retardation and movement disorder but no epilepsy
  - Minimal symptoms (adult clumsy on prolonged fasting)

Classical Early-onset GLUT1-DS

- Neonatal period may be normal
  - Breast-feeding may be protective
- In first few months
  - Seizures are main presentation
    - Cyanotic attacks
    - Eye movement seizures (mistake for opsoclonus-myoclonus)
    - Mean age seizure onset 26 weeks (neonates-77 months)
    - 79% of all first seizures in first 6 months

Classical Early-onset GLUT1-DS (2)

- Global developmental delay
  - Especially speech
- OFC decelerates after 3 months
- Complex movement disorder
  - Ataxia
  - Dystonia
  - Pyramidal tract signs
  - Paroxysmal exercise-induced dyskinesias

Diagnosis GLUT1

- CSF:Plasma ratio below 0.50 in all but one patient (range 0.19–0.52)
- Absolute CSF glucose below 2.5 mmol/l (range 0.9–2.4 mmol/l) in all patients
- Low CSF lactate
- SLC2A1 sequencing

Treatment

- Ketogenic diet
  - infancy to adolescence
- Seizures controlled at lower blood levels of beta–hydroxybutyrate than needed to nourish the brain
- Carnitine supplements

- Avoid inhibitors of GLUT1 function
  - Phenobarbitone, valproate, diazepam
  - chloral hydrate
  - Methylxanthines, caffeine, green tea
  - ethanol

Clinical Clues in metabolic epilepsy

- 4 month old of consanguineous parents
- Intractable seizures
- Apnoea, intermittent stridor
- Global hypotonia
- Alopecia
- Rash

Biotinidase deficiency

- Biotin
  - B-group vitamin
  - essential for binding to carboxylase enzymes (gluconeogenesis, amino acid metabolism and Kreb's cycle)
  - Inborn errors involve enzymes needed for biotin recycling:
    - biotinidase deficiency (biotin-responsive)
    - *holo*-carboxylase synthase deficiency (many also biotin-responsive)

Biotinidase Deficiency – Clinical features

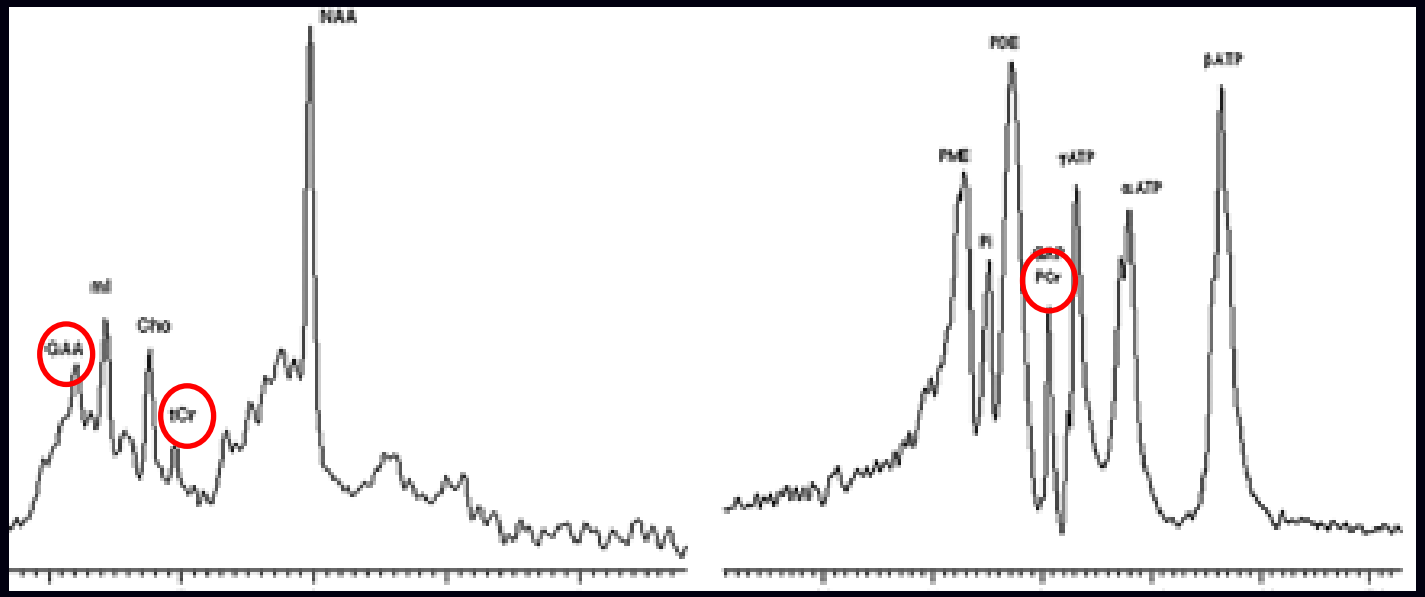
- Variable age of onset
- Most commonly neurological symptoms
  - at 3-4 months of age (can be up to 10 years);
  - epilepsy (often infantile spasms)
  - hypotonia
  - ataxia in older children
- Also
  - Dermatitis
  - Alopecia
  - Conjunctivitis
- Later
  - hearing loss
  - visual loss

Biotinidase deficiency – diagnosis and treatment

- **Diagnosis**:
  - Plasma biotinidase level (usually <10% activity)
  - Organic aciduria (because of effect on carboxylases)
  - Hyperammonaemia
  - Lactic acidosis
- **Treatment:**
  - Biotin 5-20mg/day orally
  - Prompt resolution of abnormal biochemistry, skin, seizures and ataxia
  - Hearing and visual loss irreversible

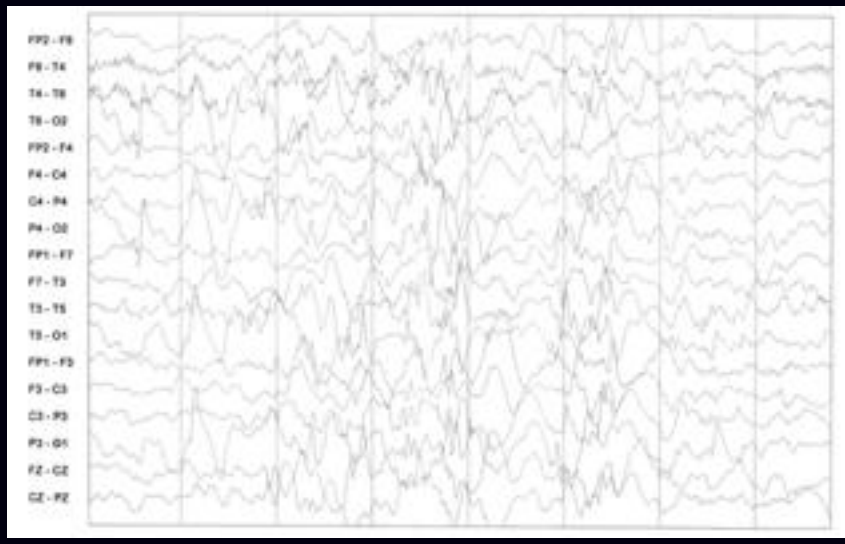
Clinical Clues in metabolic epilepsy

- Early onset epilepsy
- Severe global developmental delay
- Severe axial hypotonia
- Prominent speech delay



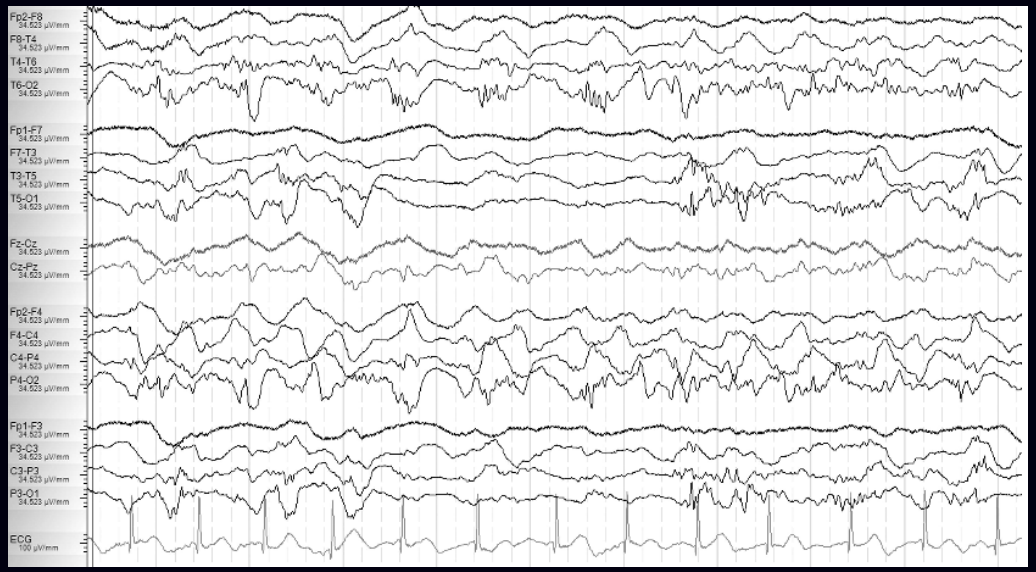
Clinical Clues in metabolic epilepsy

- Onset 3 months
- Multifocal seizures
- Evolved to infantile spasms
- Abnormal coarse hair



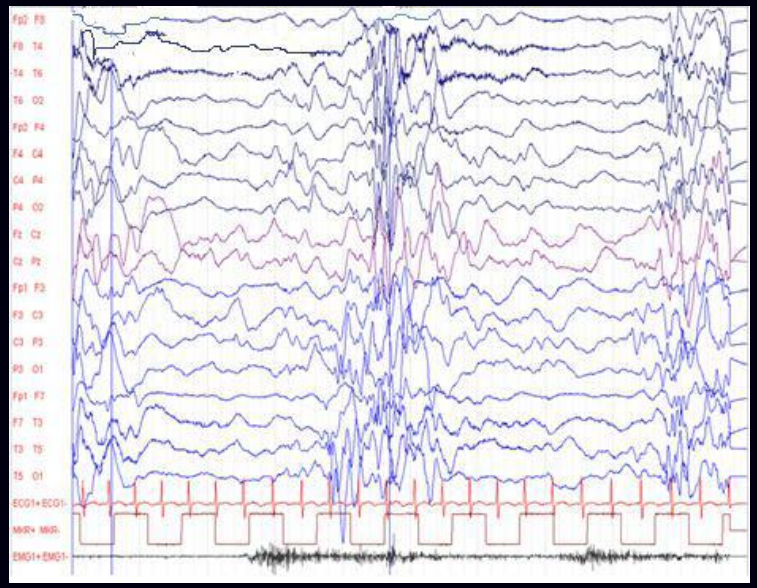
Clinical Clues in metabolic epilepsy

- Catastrophic onset of seizures from 6 weeks
- Multifocal, myoclonic
- Raised ALT
- Liver failure with sodium valproate



Clinical Clues in metabolic epilepsy

- Normal birth
- Onset of severe intractable seizures at D5
- Lethargy, encephalopathy,
- EEG



Other metabolic disorders presenting as early onset epilepsy

Serine biosynthesis defects

- Microcephaly, hypertonic, severe developmental delay.
- spasms and EEG hypsarrhythmia, (➔LGS)
- CSF amino acids
- treatment with serine (+/-glycine) at birth/in utero.
- milder clinical phenotype: late childhood onset absence epilepsy with typical EEG 3 Hz spike–wave , learning difficulties but normal OFC

- Even rarer…

- Peroxisomal disorders- Zellwegers
- Cathepsin D deficiency (congenital NCL)
- GABA transaminase deficiency

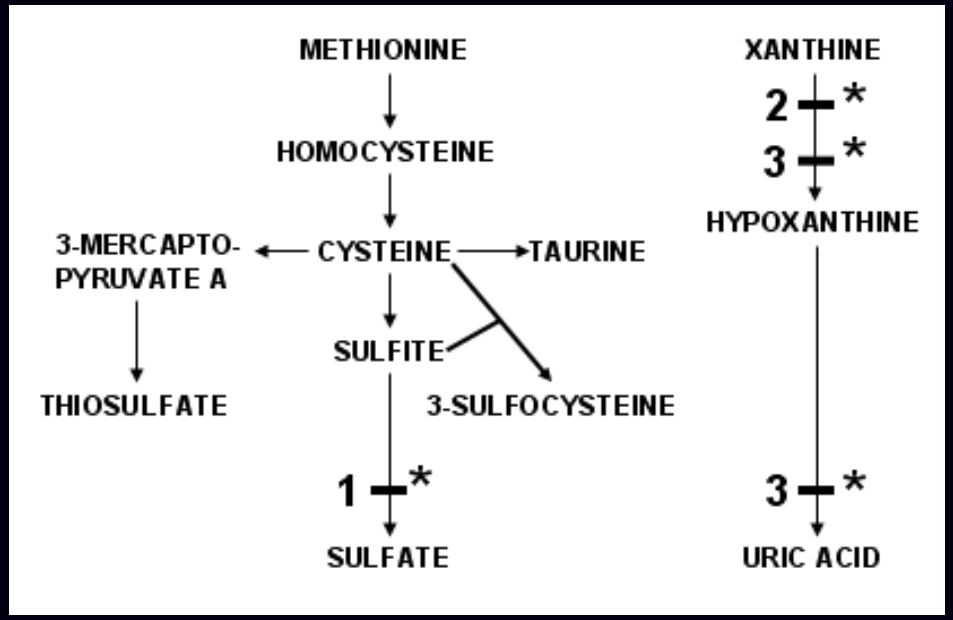
Sulphite oxidase deficiency/MoCof

MoCoF:

- Seizures, dystonia and dev delay, death in early childhood.
- Burst suppression
- Low urate, urinary sulphite or sulphocysteine, urinary purines

Isolated SO deficiency:

- Identical clinically
- Normal urate and plasma purines



Molybdenum= essential cofactor for sulphite(1) and aldehyde oxidases (2) and for xanthine dehydrogenase(3)

Later treatable childhood presentations with epilepsy

- Creatine transport deficiencies- GAMT
- Cerebral folate deficiency- seizures, novement disorder, low CSF 5-MHTF and response to folinic acid, primary and secondary causes
- Co-enzyme Q deficiency- nephropathy, hearing loss, nystagmus, ataxia, dystonia
- PDH- treatable with KD

Mitochondrial epilepsy

- MELAS, MERRF and other mtDNA mutations
- POLG mutations (Alpers and later onset epilepsies)
- COX I deficiency
- CoQ10
- RARS2

Epilepsy phenotypes:

- Neonatal refractory status and multiorgan failure
- Neonatal myoclonic epilepsy
- Infantile spasms
- Refractory/recurrent status epilepticus
- EPC
- (Progressive) Myoclonic epilepsy

Progressive Myoclonic Epilepsy Work-up

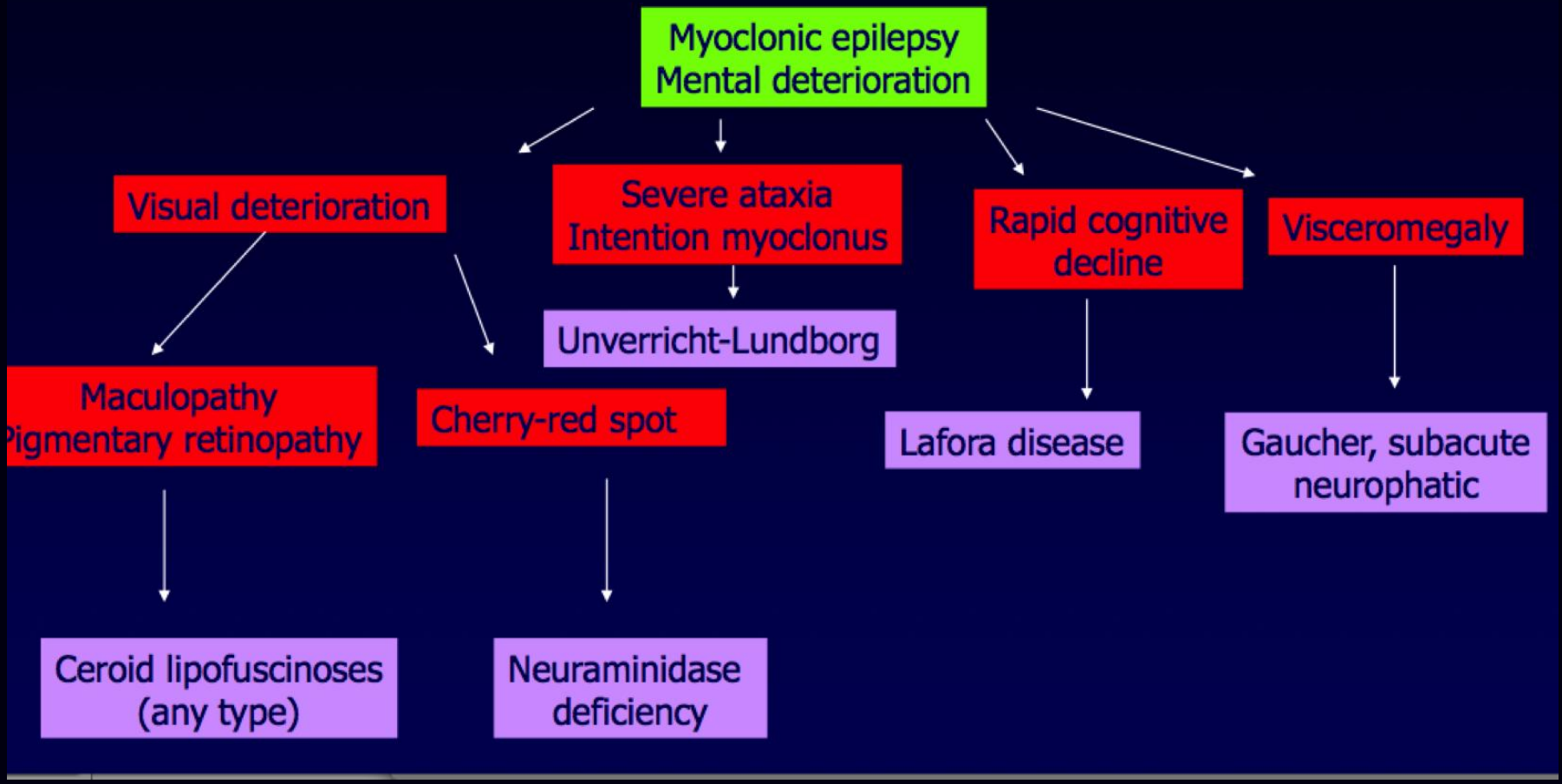


Table 1 Main differentiating features of some of the more common inherited progressive myoclonic epilepsies.

Progressive myoclonic epilepsy	Inheritance	Onset (years)	Suggestive clinical signs	Pathologic features	Gene
Unverricht–Lundborg disease (EPM1)	AR	6–15	Slow progression; mild and late cerebellar impairment; late or absent dementia	None	*CSTB* (*PME*)
Lafora disease (EPM2)	AR	6–19	Visual symptoms	Polyglucosan inclusions (Lafora bodies)	*EPM2A* *EPM2B* (*NHLRC1*)
MERRF	Maternal	Any age	Lactic acidosis	Ragged red fibers	*MT-TK* (*tRNALys*)
NCLs	AR or AD	Variable	Macular degeneration and visual impairment (except adult form)	Lipopigment deposits and granular osmiophilic, curvilinear, or fingerprint inclusions	*CLN1* (*PPT1*), *TPP1* (previously *CLN2*), *CLN3–CLN6*, *MFSD8* (previously *CLN7*), *CLN8*, *CLN9*
Sialidoses	AR	8–15	Gradual cerebellar impairment; cherry red spot maculopathy	Urinary oligosaccharides, and fibroblast neuraminidase deficit	*NEU1*

Abbreviations: AD, autosomal-dominant; AR, autosomal-recessive; MERRF, myoclonic epilepsy with red ragged fibers; NCLs, neuronal ceroid lipofuscinoses.

Other important metabolic disorders in late childhood/adolescence

LSD's:

- Gaucher- SNGP, dementia, extrapyramidal symptoms
- Type 1 sialidosis- cherry red spot myoclonus syndrome
- NPC- late onset forms with hepatosplenomegaly and vertical SNGP, Miglustat
- Juvenile NCL

Biochemical Markers of IEM

- Full neurometabolic screen
- Plasma
- Urine
- CSF
- Clues to diagnosis

- Confirmatory genetic studies

Routine Clinical Chemistry

Investigation	Abnormality	Inborn error of metabolism associated with infantile epilepsy
Glucose	Low	FAO Glycogen storage disorders Disorders of gluconeogenesis
Ammonia	High	Urea cycle defect Organic acidaemias
Lactate	High	PDH deficiency Mitochondrial respiratory chain defects Biotinidase deficiency
LFTs	High	Alpers Mitochondrial depletion syndrome
CK	High	Dystroglycanopathies

Specialised Blood Investigations

Investigation	Abnormality	Disorder
Amino Acids	High glycine High glycine/threonine Low serine High phenylalanine	NKH PNPO/PDE Serine biosynthesis Untreated PKU
Urate	Low	Molybdenum cofactor deficiency
Copper/caeruloplasmin	Low	Menkes
VLCFA	High	Peroxisomal
Biotinidase	Low	Biotinidase deficiency
TIEF	Abnormal glycoforms	CDG
White cell CoQ	Low	CoQ10 biosynthesis disorders Mitochondrial disorders
Vacuolated lymphocytes	Present	Lysosomal storage disorders NCL

Urine Metabolic Investigations

Investigation	Abnormality	Disorder
Organic acids	Vanillactate Specific organic acids Krebs cycle intermediates	PNPO deficiency Organic acidaemias Mitochondrial defects
Sulphite	High	Sulphite oxidase deficency MoCoF deficiency
Guanidinoacetic acid	High	GAMT
Creatine	Low High	GAMT Creatine transporter deficiency
αAASA	High	PDE
Purine/Pyrimidines	Hypoxanthine Succinyladenosine	MoCoFdeficiency Adenylosuccinate lyase deficiency

CSF Investigations

Investigation	Abnormality	Disorder
Glucose	Low	GLUT1
Lactate	High	Mitochondrial PDH deficiency
Amino acids	High glycine Low serine High threonine/glycine	NKH Serine biosynthesis disorders PNPO/PDE
PLP	Low	PDE/PNPO
5-MTHF	Low	DHFR deficiency FOLR1 Kearns-Sayre Other mitochondrial MTHFR deficiency

Treatments

IEM and Age of Epilepsy Presentation

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IEM and Treatments

- Established therapies

PDE	Pyridoxine
PNPO	Pyridoxal phosphate
Biotinidase deficiency	Biotin
GLUT1	Ketogenic diet
Creatine disorders	Creatine
Cerebral folate deficiency	Folinic acid

IEM and Treatments

- Experimental treatments

Menkes	Copper injections
NKH	Benzoate/Dextromethorphan
GAMT	Ornithine supplementation
PDE	Lysine restriction

- Gene therapy

Conclusion

- IEM are a relatively rare cause of EIEE and later childhood epilepsy
- Diagnosis is made on clinical grounds
- Supportive biomarkers in metabolic testing
- Diagnosis important
- Therapeutic options
- Prompt treatment may affect long term outcome
- Implications for genetic counselling

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