Fits and Seizures

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To be discussed today

- Introduction
- Case studies
- Outline of the Guidelines

Fits

- 3% of general population have epilepsy at some time in their lives
- Most common inherited forms of epilepsy due to channelopathies
- Fits can be associated with febrile disorders
- Intercurrant illness can provoke a metabolic crisis in affected patients

Initial investigations

- Seizure type,
  - focal , usually the result of CNS insult
  - Generalised
- EEG pattern
- Initial biochemistry

First Line Investigations

- sodium, potassium and calcium (plasma)
- blood gases
- blood ammonia
- urine amino and organic acids
- bloodspot acyl carnitines
- plasma and CSF lactate and amino acids
- urate (plasma)

Neonatal Fits, case 1

- Male, second cousin parents
- Uncomplicated pregnancy
- Ultrasound scan at 23 weeks gestation - normal foetus
- Uncomplicated normal delivery at 39 weeks, good condition.

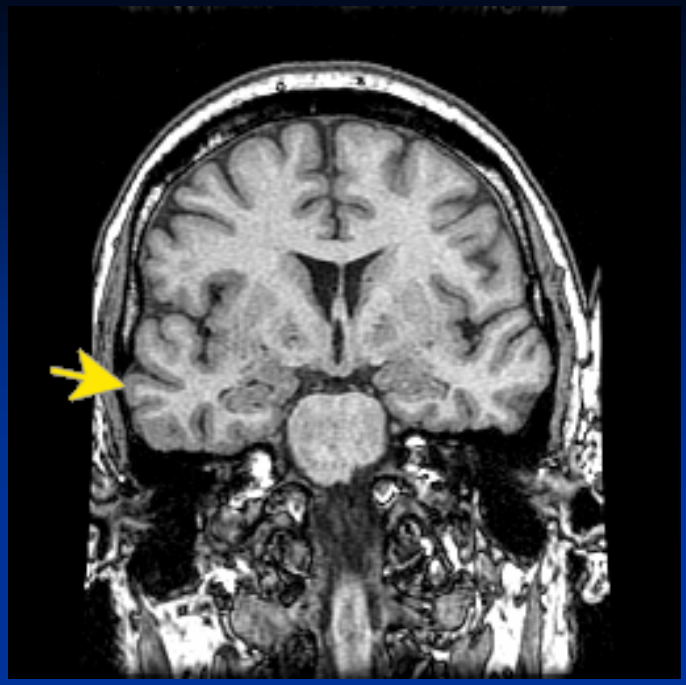
Post-partum

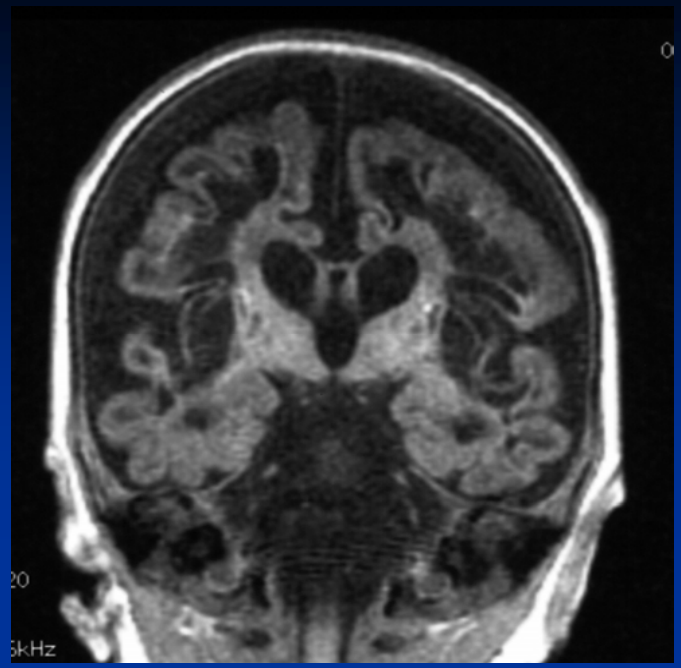
- 12h post partum – abnormal movements, high pitched cry, lethargy, hypertonic, pyrexial, not suckling and fits by end day 1
- admitted to SCBU

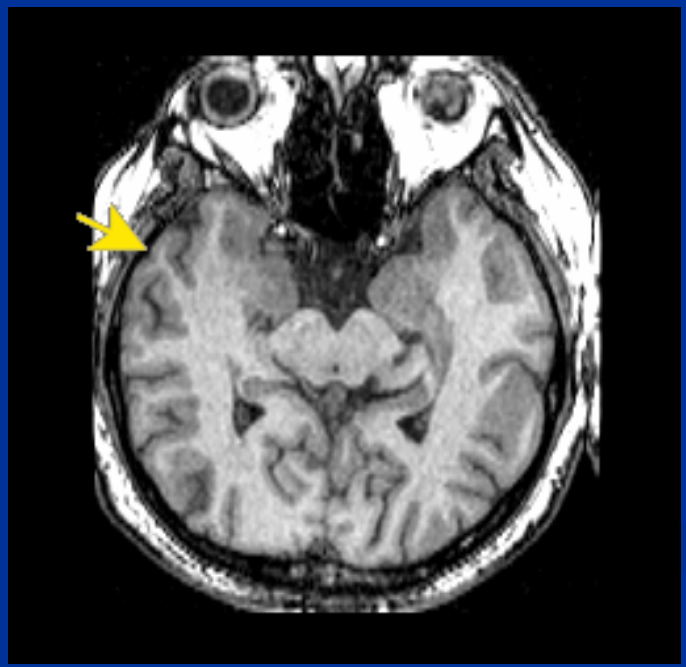
Initial investigation

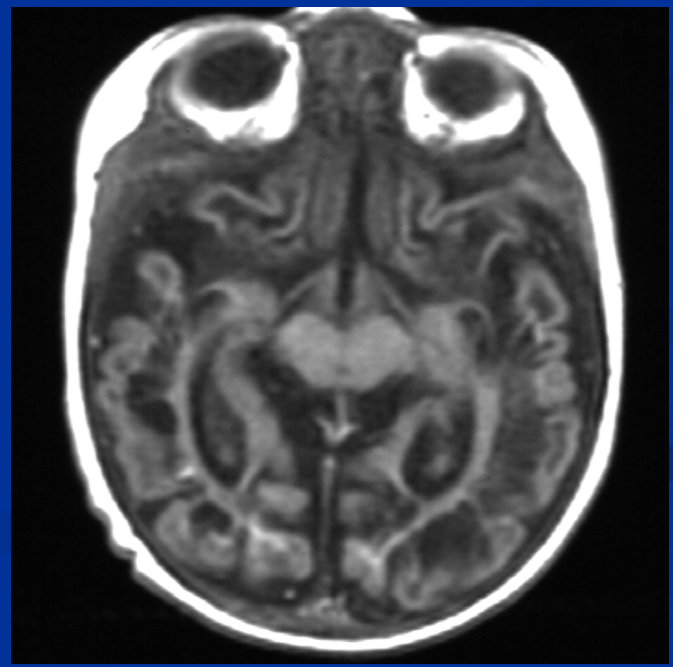
Na^+	148
K^+	5.7
Urea	4.9
Creat.	108
Alb	37
Adjust. Ca^{2+}	2.26
Phosphate	2.45
Mg^{2+}	0.80
CRP	6.0

Started on iv fluids (105ml/kg 10% dextrose) and antibiotics (Benzylpenicillin and Cefatoxime).









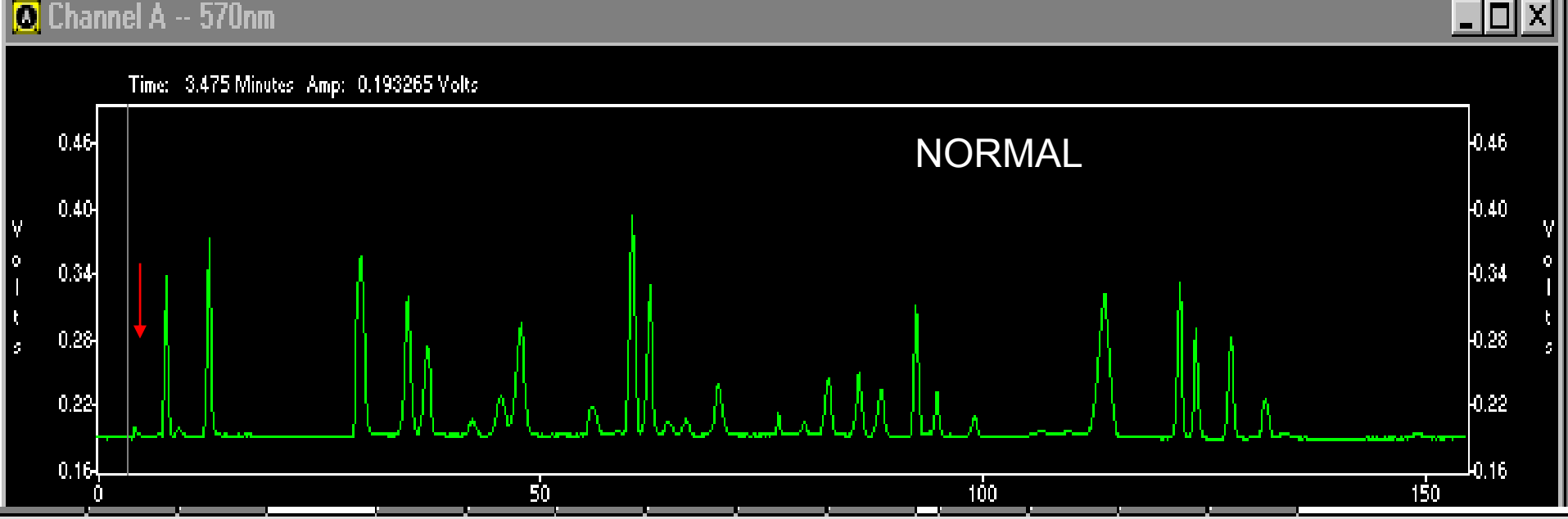
- condition worsened and seizures became more frequent.
- Unresponsive to phenobarbitone or phenytoin
- Microbiology all normal including CSF cultures.

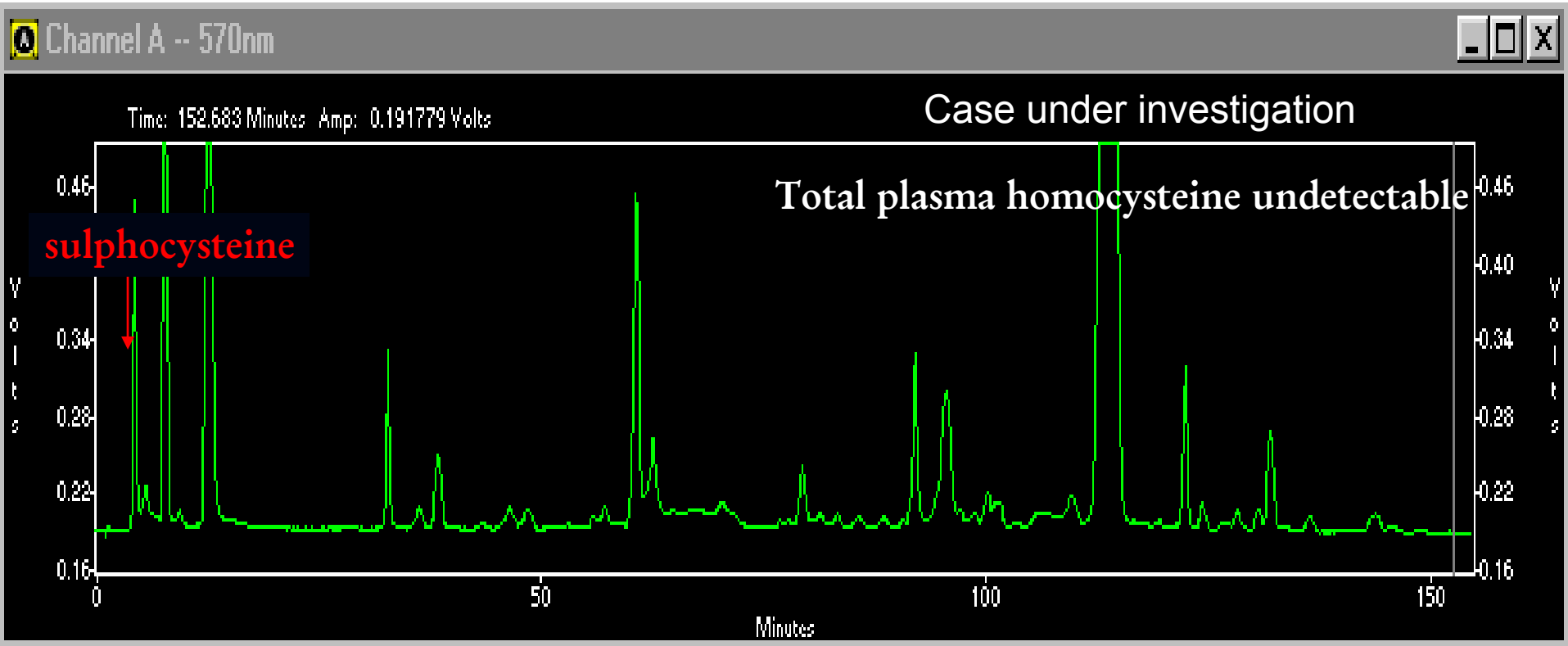
CSF glycine:plasma	normal
Ammonia	113 µmol/L
Lactate	3.78 mmol/L
Acylcarnitine	Normal profile
Serum urate	27 µmol/L (200 – 450)

Urine purines

Urate	0.000 mmol/L
Hypoxanthine	0.112 mmol/L
Xanthine	2.076 mmol/L
Urate/Creat ratio	0.00 (0.30-1.50)

- Results consistent with xanthine oxidase deficiency.


Channel A -- 570nm
Time: 3.475 Minutes Amp: 0.193265 Volts
NORMAL
Volts
0.46
0.40
0.34
0.28
0.22
0.16
0
50
100
150


Channel A -- 570nm
Time: 152.683 Minutes Amp: 0.191779 Volts
Case under investigation
Total plasma homocysteine undetectable
sulphocysteine
Volts
0.46
0.40
0.34
0.28
0.22
0.16
0
50
100
150
Minutes

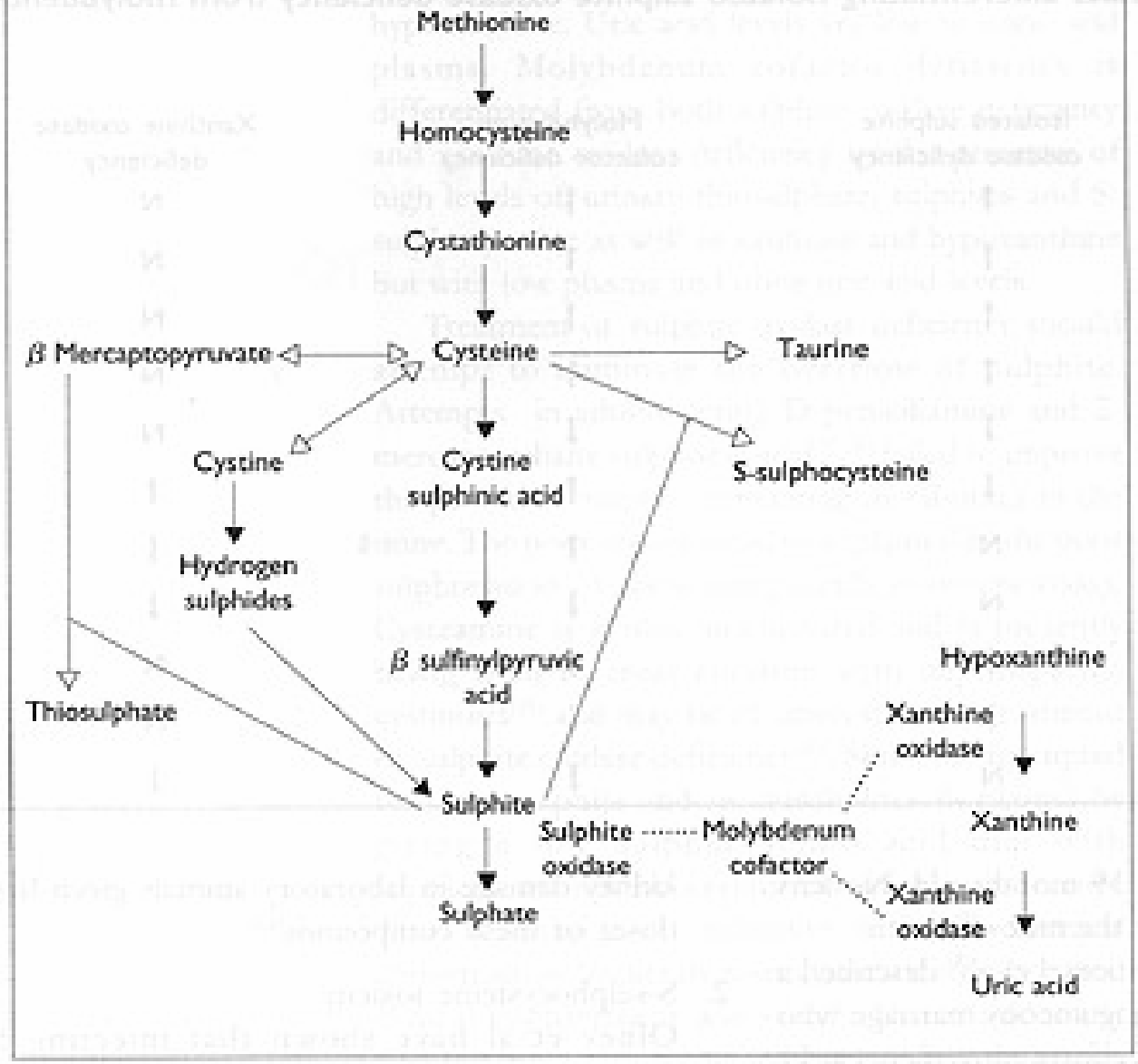


Fig 1 - Metabolic pathway of sulphur amino acids to sulphite and sulphate

Treatment

- No effective therapy available
- Diet ineffective in neonatal form
- Instability of molybdenum cofactor precludes its use

- Child died at 10 months

Case 2

- unrelated parents
- term baby, no recorded neonatal problems
- severe persistent fitting from day 2
- early apnoea, lactate 8 mmol/L
- no evidence of hyperammonaemia, hypoglycaemia
- urine organic acids & blood acyl carnitines: NAD
- plasma and urine sulphocysteine present
- died at 3 weeks

Results summary

Date	Urine						Plasma			
	sulfocys	taurine	cystine	glycine	sulphite		sulfocys	taurine	cystine	glycine
ref value	*ND*	*<1051*	*<37*	*<938*	*neg*		*ND*	*92-392*	*21-73*	*220-527*
6.8.00	139	448	3	504	neg		40	76	ND	244
14.8.00							55	298	ND	449
15.8.00							46	308	ND	412
17.8.00	356	1067	19	2070	pos		44	319	ND	438
22.8.00							60	112	ND	288
24.8.00	304	2087	6	557	neg		40	148	ND	256
25.8.00	367	2404	11	591	neg					

Purine Metabolism

- Plasma urate: 0.18 *(ref 0.14-0.26)*
- Urine urate:creatinine: 1.18 & 0.71 *(ref 0.43-1.52)*
- Report from Purine Lab at Guy's:

no evidence of molybdenum cofactor deficiency

Subsequent Sibs

Next pregnancy

- Affected

Next

- Unaffected
  - Healthy baby during neonatal peroid
  - Had fit aged 10 months
  - Continues to have seizures, ? aetiology

National Metabolic Biochemistry Network
Best Practice Guidelines

The Biochemical Investigation of Fits and Seizures for Inherited Metabolic Disorders

www.metbio.net

Guideline format

- Introduction
- First line tests
- Second line tests, including leukocyte enzyme panel
- Tables of other conditions to consider, i.e. assuming more easily tested disorders excluded

Disorder	Supporting Clinical Signs	Test
Neonatal/early onset	**Presentation**	
Peroxisomal defects of β-oxidation and organelle genesis	dysmorphism, hypotonia, liver dysfunction	plasma very long chain fatty acids
Biotinidase deficiency	alopecia, skin rashes, hypotonia	plasma biotinidase
Non ketotic hyperglycinaemia	hypotonia, apnoea, burst-suppression EEG	plasma and CSF glycine
3-Phosphoglycerate dehydrogenase deficiency	microcephaly, psychomotor retardation	plasma and CSF serine
Molybdenum cofactor deficiency	lens dislocation	urine and plasma low urate urine and plasma sulphocysteine undetectable plasma homocysteine
isolated sulphite oxidase deficiency	lens dislocation	urine and plasma sulphocysteine undetectable plasma homocysteine
Glutaric acidaemia type 1	macrocephaly, dystonia	urine organic acids and bloodspot acylcarnitines are not always positive, It may be necessary to assay the enzyme in cultured fibroblasts
GLUT 1 deficiency		CSF glucose (low) (ratio to plasma)
Homocystinuria, remethylation defects	hypotonia, micocephaly	plasma total homocysteine
γ-Aminobutyrate transaminase deficiency	psychomotor retardation, hypotonia	CSF GABA*
Aromatic amino acid decarboxylase deficiency	mental retardation, movement disorders, hypotonia, recurrent hyperthermia, hypersalivation, bulbar symptoms, temperature instability	Urine vanillylactic acid increased CSF Neurotransmitters, HVA, HIAA and dopamine low *
Pyridoxine responsive seizures	responds to pryidoxine may take up to four weeks more rarely	urine vanillactic acid may be increased and CSF Neurotransmitters may be abnormal, but testing not usually indicated
Pyridoxal Phosphate responsive seizures	pyridoxine unresponsive but responds to pyridoxal phosphate	CSF amino acids: raised gly, threo, his

Later infancy/early childhood	Presentation	
Purine and pyrimidine disorders	Psychomotor retardation, Cerebellar hypoplasia, Microcephaly, feeding difficulties	urine purines and pyrimidines
Carbohydrate deficient glycoprotein disorders	unusual distribution of sub cutaneous fat, strokes, ataxia, atrophy of cerebellum, clotting abnormalities. dysmorphism.	plasma transferrin isoforms
CLN 1,2 (Batten's Disease)	visual loss, retinitis pigmentosa, dementia	CLN1 leucocyte palmitoyl protein thioesterase CLN2 leucocyte tripeptidyl peptidase I skin biopsy may be necessary
Creatine synthesis disorders - (GAMT) Guanidinoacetate Methyltransferase - (AGAT) Arginine:glycine amidinotransferase	mental retardation, speech delay, extrapyramidal symptoms	low plasma and urine creatinine. Definitive test is brain MRS for creatine. Plasma and urine guanidinoacetate elevated in GAMT deficiency and reduced in AGAT deficiency.
Creatine transporter defect	Mental retardation, speech delay	Definitive test is brain MRS for creatine Increased creatine:creatinine ration in urine

Later childhood – in addition to the above		
Gaucher disease type 3	hepatosplenomegaly, dystonia.	Plasma chitotriosidase (non-specific). Leucocyte beta-glucosidase
Lafora disease	intellectual decline and early death	demonstration of storage material in tissue biopsy
Disorders of folate metabolism		discuss with your specialist laboratory – see metabolic assay directory
CLN3 (Juvenile Battens Disease)	Visual loss, retinitis pigmentosa, dementia	DNA analysis for common deletion.
Acute porphyrias	Presentation usually after puberty, acute abdomen, pyschosis	Urine PBG


THE
END