**The “easy” metabolic diagnoses**
- detected on routine metabolic testing
  - "urine metabolic screen"
    - ketones, protein, blood, glucose
    - amino acids
    - total glycosaminoglycans
    - organic acids - ONLY if requested / indicated
- associated other abnormalities
  - hypoglycaemia, acidosis, hyperammonaemia

**Seizures and hypoglycaemia**
- Glycogen storage diseases
- Fructose 1,6-bisphosphatase deficiency
- Hereditary fructose intolerance
- Organic acidaemias
  - propionic, methylmalonic, isovaleric

**Seizures and metabolic acidosis**
- PDH complex deficiency
- Mitochondrial encephalomyopathies
- Multiple carboxylase deficiency disorders
  (a.k.a. biotinidase deficiency)
- Intermittent maple syrup urine disease
- Organic acidaemias
  - propionic, methylmalonic, isovaleric
- Glutaric aciduria

**Seizures and hyperammonaemia**
- Early onset biotinidase deficiency
- Carnitine palmitoyltransferase def type 1
- Hyperammonaemia-ornithinaemia- citrullinuria disorder
- Organic acidaemias
  - propionic, methylmalonic
- Oxidative metabolism disorders
- Urea cycle defects

**The “easy” metabolic diagnoses**
- aminoacidopathies
  - maple syrup urine disease
- organic acidaemias
  - isovaleric, propionic & methylmalonic aciduria
  - succinic semialdehyde dehydrogenase deficiency
- urea cycle defects
  - OTC deficiency, ornithinaemia, arginosuccinic aciduria, carnitine palmitoyltransferase deficiency
- fatty acid oxidation disorders
  - MCAD deficiency
- defects of carbohydrate metabolism
  - galactosaemia, GSD type 1, fructose intolerance

**Difficult diagnoses**
- routine biochemistry normal
- routine metabolic screen normal / nonspecific
- specific diagnostic test required
- all very rare conditions
• GLUT-1 deficiency syndrome (paired CSF and blood glucose)
• pyridoxine (pyridoxal phosphate) dependent seizures (2-AASA)
• folinic acid responsive neonatal seizures (folinic acid)
• late onset biotinidase (multiple carboxylase) deficiency (biotin)
• selenium deficiency (selenium)
• disorders of creatine metabolism (MRS reduced brain creatine)
• nonketotic hyperglycinemia (CSF amino acids - glycine)
• molybdenum cofactor & sulfite oxidase deficiency (plasma AA)
• adenylosuccinase deficiency (HPLC urine purines/pyrimidines)
• neonatal ALD & other peroxisomal disorders (VLCFA)
• GABA transaminase deficiency (CSF amino acids - GABA)
• 3-phosphoglycerate dehydrogenase deficiency (low CSF serine)
• carbohydrate deficient glycoprotein syndrome (transferrin)
• mitochondrial encephalomyopathies (CSF, MRI/S, genes, bx)
• Menkes kinky hair disease (low copper, caeruloplasmin)
• neuronal ceroid lipofuscinosis I and II (lysosomal enzymes)
• other lysosomal disorders with leukodystrophy (CSF protein)
• Alpers disease – progressive poliodystrophy (CSF protein, POLG)

Glucose transporter protein syndrome
• GLUT-1 protein
• blood-brain barrier hexose carrier
• seizures, acquired microcephaly, ataxia, mental retardation, hypotonia, movement disorder
• diagnosis - persistent low CSF glucose (CSF:plasma ratio <0.36 (normal = 0.6))
  - Glut1 gene testing
• treatment = ketogenic diet - alternative brain energy source

Pyridoxine dependent seizures
• autosomal recessive, several gene defects
• defect of pyridoxal phosphate dependent glutamic acid dehydrogenase activity (proposed)
  • ↓ GABA : lowered seizure threshold
  • ↑ glutamate: excitotoxicity, ? mental retardation

Additional tests to allow diagnosis in most cases
• trial of pyridoxine
• paired (same time) plasma and CSF
  • glucose and lactate
  • amino acids - especially glycine, GABA, serine
  • urine organic acids and fresh sulfite dipstick
  • urine pyrimidines / purines
  • plasma VLCFAs
• CSF protein - often ignored
• CSF biogenic amines
• transferrin immuno-isoelectric focusing