New Disorder of Serine / Glycine Biosynthesis: Phosphoserine Aminotransferase (PSAT) Deficiency

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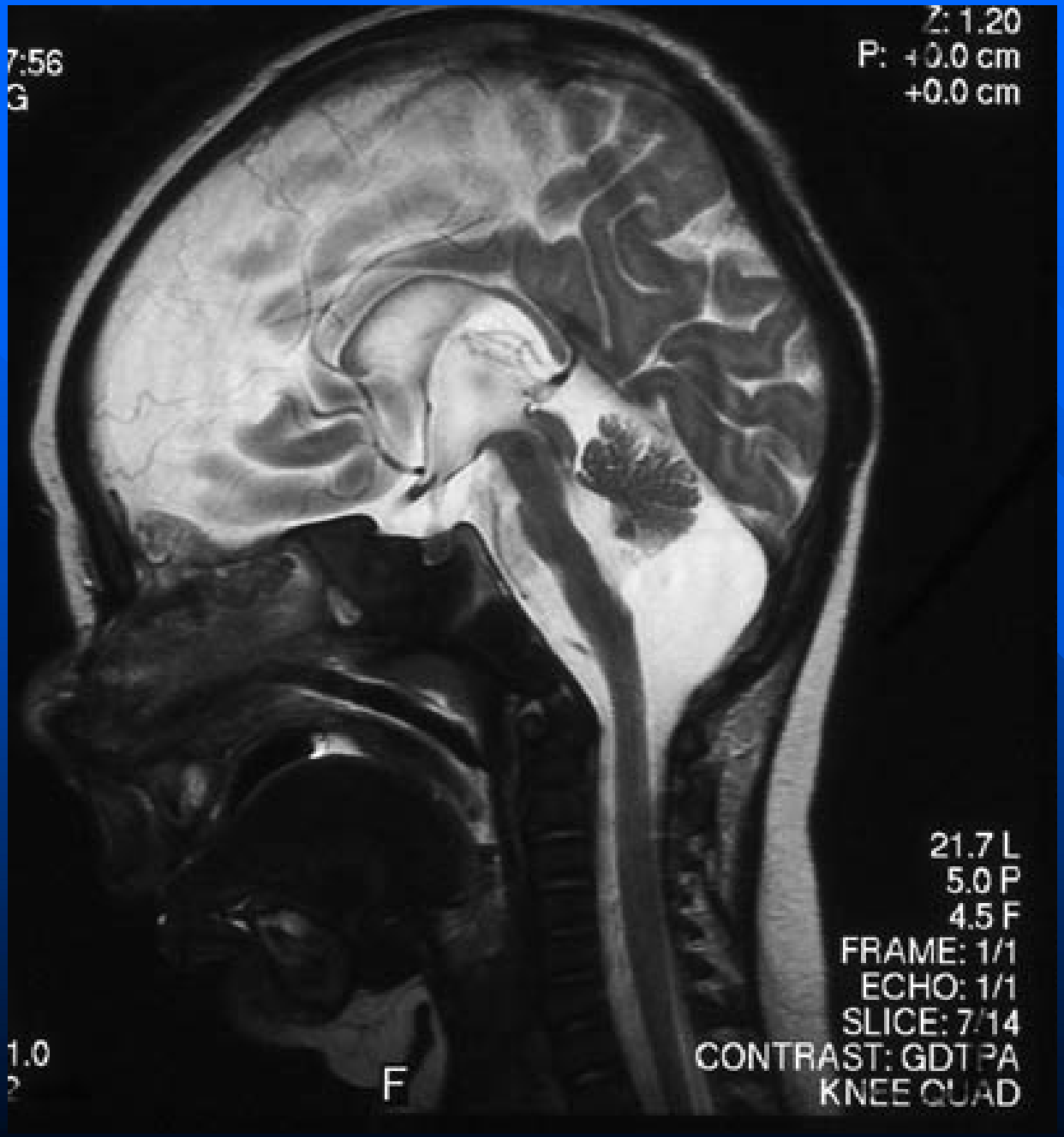
Case 1

- Male, second child of healthy, unrelated parents of British origin
- Well at birth but presented at 9 weeks with frequent, severe, intractable seizures and hypertonia
- HC had dropped from 9th to <0.4th centile
- MRI scan showed general atrophy, hypoplastic cerebellar vermis and poor white matter development
- EEG consistent with multifocal seizure activity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Case 1

- Extensive biochemical investigations, only abnormalities were;

-Plasma serine = 51 (60-300) µmol/L

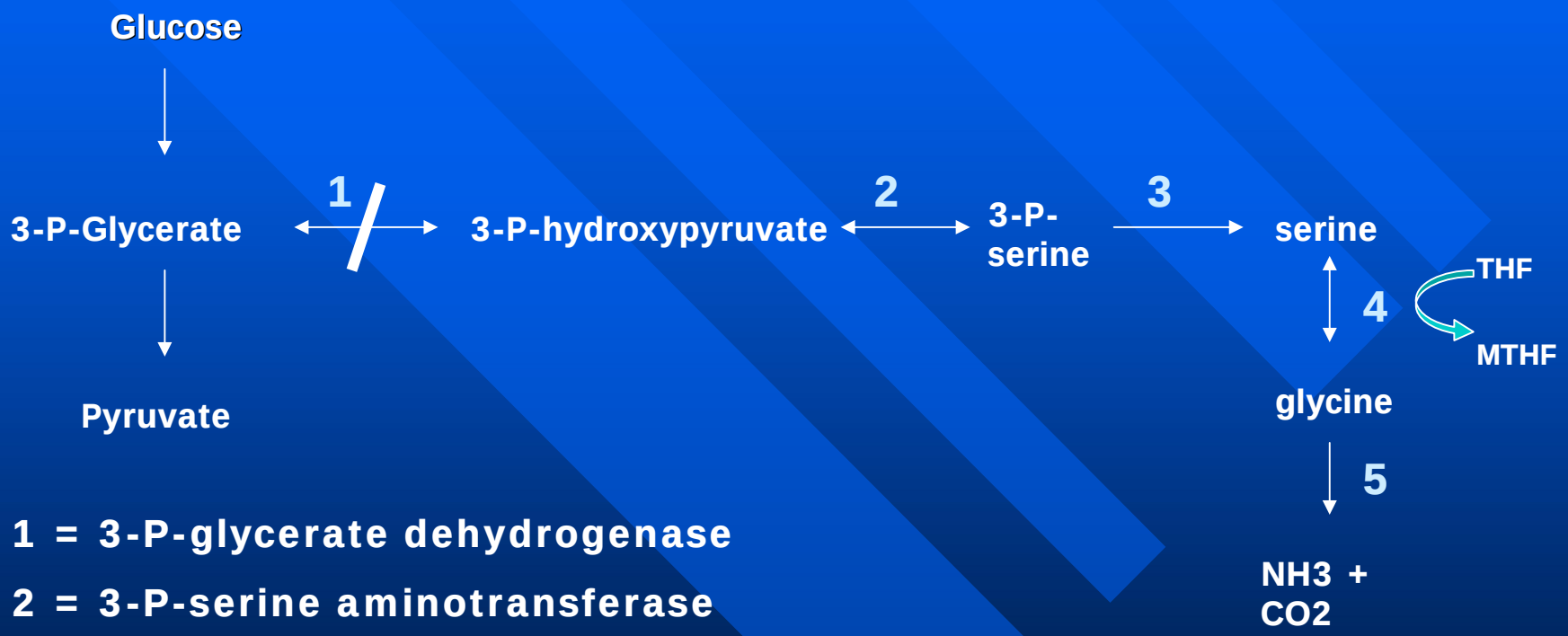
-Plasma glycine = 121 (140-420) µmol/L

CSF serine = 18 (35-80) µmol/L

CSF glycine = <1 (0-10) µmol/L

? 3-Phosphoglycerate Dehydrogenase Deficiency

Serine and Glycine Biosynthesis



1 = 3-P-glycerate dehydrogenase

2 = 3-P-serine aminotransferase

3 = 3-P-serine phosphatase

4 = serine hydroxymethyl transferase

5= Glycine cleavage system (NKH)

- Skin biopsy taken for enzyme assays
- Treatment with serine (500 mg/kg) and glycine (200 mg/kg) started at 11 weeks, normalising plasma and CSF levels
- Limited effect on seizures, still having severe seizure episodes requiring PICU admission
- Became increasingly hypertonic, condition deteriorated, died at 7 months of age

Enzyme Results

- 3-PGDH = 70 mU /mg protein (controls = 25 ±2.6)
- PSAT = 0.9 (controls = 2.0 ± 0.3)
- PSP = 2.4 (controls = 1.5 ±0.2)

- Essentially normal results!

Case 2

- Sister of Case 1
- Monitored before birth, fetal growth and development appeared normal
- Blood sample taken at 2 hrs of age;
  Serine = 30 (50-350) µmol/L
  Glycine = 110 (200-600) µmol/L
- CSF -serine = 5 (35-80) µmol/L
  -glycine = <1 (0-10) µmol/L

- Supplementation with serine / glycine normalised plasma and CSF levels
- HC was on 9th centile at birth, increases to 50th-75th by week 18
- Cranial US at 3 weeks and MRI at 4 months showed no abnormality
- Experienced an apnoeic episode at 2 weeks, otherwise asymptomatic
- Developing normally at 3 yrs of age

Enzyme Assay

- Only 3-PGDH measured,

  11.6 mU / mg protein (controls = 29.5 ± 2.7, affected = 6.6, 3.7)

  Because these enzyme assays are problematic the decision was made to use mutational analysis to investigate further

Mutational Analysis

- No mutations in genes for 3-PGDH or 3-PSP
- Both children compound heterozygotes for mutations in the PSAT gene
- One frame shift mutation –c.del G107
- One missense mutation –c.299A>C, p.Asp100Ala

Missense Mutation –pathogenic?

- Replaces a well conserved aspartate residue with alanine
- Comparison with the crystal structure of *E. Coli* PSAT indicates a loss of hydrogen bonding between loops when aspartate is replaced by alanine that would be expected to have a deleterious effect on protein folding
- Expression studies produced a yield of mutant protein 10 fold lower than the wildtype, with a V_{max} of about 15% of that of the wildtype

PSAT Deficiency

- Low plasma and CSF serine and glycine
- Acquired microcephaly
- Severe, intractable seizures
- Hypertonia
- psychomotor retardation

- This is a severe neurometabolic disorder with a poor outcome unless treatment is started presymptomatically

Conclusions

- The first two cases of PSAT deficiency have been identified
- Clinical features are very similar to 3-PGDH deficiency, except that the microcephaly is acquired not congenital
- Case 2 confirms the experience of de Koning et al that serine / glycine disorders can be treated very successfully provided treatment begins presymptomatically

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