EMORY GENETICS LABORATORY

Movement Disorder in a Patient with Cobalamin E Disease

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Introduction

Cobalamin (Cbl) E (MIM 236270) disease:

- Inborn error of intercellular cobalamin metabolism
- Autosomal recessive disorder
- Caused by mutations in the *MTRR* gene
- Presents as megaloblastic anemia and neurological manifestations

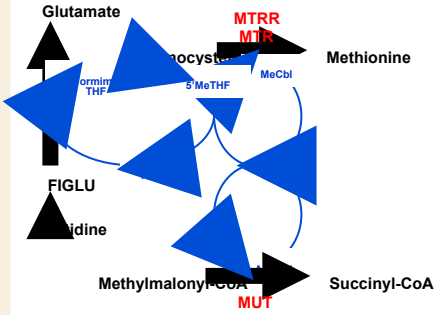


Figure 1: Pathways that interact with Cbl metabolism:

Cbl is necessary for homocysteine, histidine and methylmalonyl-CoA catabolism.

Patient History

- No family history
- No consanguinity
- Normal developmental till 11 years of age

- At 11 years of age:
  - Macrocytic anemia
  - Develops Sydenham Chorea; never fully recovers
  - Urinary incontinence
  - Regresses: needs special education classes
- At 16 years of age:
  - Misdiagnosed with absence seizures
  - Evaluated by neurologist
    - Told parents she was faking illness
- At 17 years of age:
  - Fatigue, vomiting, and reduced appetite
  - Mental status change and flat affect
  - Poor comprehension and coordination
  - Lower extremity weakness and broad-based gait
  - Peripheral neuropathy and cerebral volume loss

Analyte	Patient Result	Normal Range
Vitamin B6	17 nmol/l	20-125
Vitamin B12	253 pg/ml	210 – 911
Folic Acid	17 ng/ml	5.4-40.0
Hemoglobin	9 mg/dl	12-16
MCV	140 FL	80-100
Bilirubin	3.6 mg/dl	0-1.3

Biochemical Findings

Plasma Analytes	Patient Result (µmol/l)	Normal Range (µmol/l)
Methionine	7	21-41
Free Homocysteine	18	0
Total Homocysteine	362	4.7-11.3
FIGLU	2	0-0.1
Histidine	38	41 – 125
Methylmalonic acid	0.12	0.05-0.37

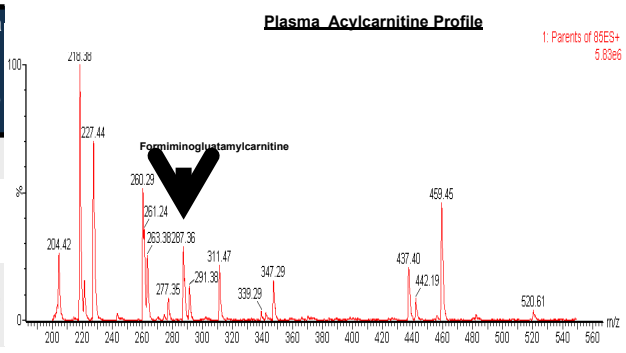


Figure 2: Plasma acylcarnitine profile preformed by LC-MS/MS shows elevated formiminoglutatamylcarnitine (FIGLU) (arrow).

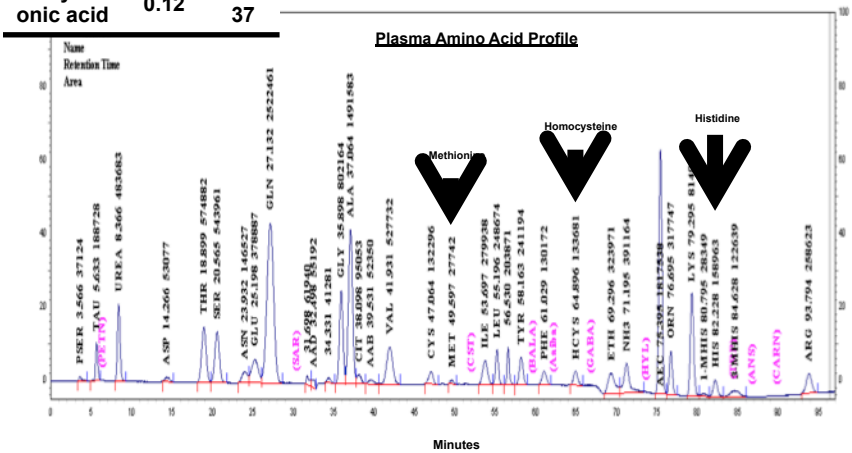
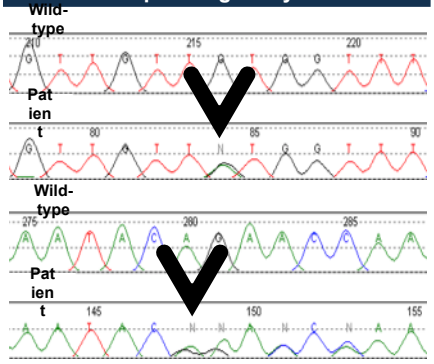


Figure 3: Plasma amino acid profile as determined by the amino acid analyzer shows elevated free homocysteine, slightly elevated histidine, normal methylmalonic acid and reduced methionine.

Sequencing Analysis



- Figure 4: Top shows a deleterious missense mutation, c.116G>A (p.V56M). Bottom shows a novel frameshift mutation, c.230delA (p.Q77RfsX34) .

Treatment and Follow up

- Treated with intramuscular hydroxocobalamin, oral betaine, pyridoxine and folic acid

- After three months of treatment:
  - resolved her anemia
  - improved memory, behavior and schoolwork
  - gait and coordination not resolved

Conclusions

- In view of normal blood level of folate and B12, FIGLU may be a biomarker for inborn errors of cobalamin metabolism.

- Patients with movement disorders and macrocytic anemia should be screened for inborn errors of cobalamin metabolism.

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