

# Organic Acidemias

Case Study by

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**FOD/OAA Family Support Groups  
National Metabolic Conference  
Atlanta, Georgia  
July 30 & 31, 2010**

# *Topics Discussed*

Case Study.

Pathophysiology of Propionic Acidemia.

Dietary Management (to be discussed by Dr Singh).

Medical Management.

Comparison to Methymalonic Acidemia.

# Case Presentation

Diagnosed through positive newborn screen.

Newborn screen was done by StepOne as the baby was born in a military family.

Newborn screening results:

C3: 18.76  $\mu\text{mol/L}$

C3/C2 ratio: 0.95

C3/C16: 5.54

Confirmatory diagnostic studies.

# Confirmatory Testing

- Acylcarnitine Profile: C3 of 19.21  $\mu\text{mol/L}$
- PCCB gene sequencing:
  - Two copies of a c.1477delC single nucleotide deletion mutation were detected.
  - Not reported previously.
  - Predicted to cause disease.

- Dietary intervention was implemented within 7 days of newborn screening results.
- Patient was started on:
  - Propimex-1.
  - Similax Advance.
  - Biotin.
  - Carnitine.

(Dr Rani Singh to discuss further)

- At 2 months visit:
  - Difficulty gaining weight (<5<sup>th</sup> percentile).
  - Constipation.
  - No metabolic decompensations.
  - One episode of vomiting.
  - Complicating social factors include:
    - Teenage mother.
    - 4 hour away from a metabolic center.

## On 9 month visit:

G-tube placed at 7 months of age with active involvement of the pediatrician.

Multiple admissions for vomiting and hyperammonemia.

No longer able to hold head and hold his bottle.

Admitted on the day of visit because of vomiting.

- On 13 month visit:
  - G-tube replaced once.
  - Also started on Iron tablets because of persistent anemia.
  - Does not sit, stand, crawl or walk.
  - Does not say any words.
  - Floppy.
  - Zofran prescribed for persistent nausea.

# Present Clinical Condition

- Despite optimal dietary therapy patient has had a difficult course.
- At 7 months of age had a G-tube placed to better manage his dietary plan.
- Continues to have frequent medical admissions secondary to metabolic decompensations.
- Developmentally delayed.

# Present Management

- Gets Physical, Occupational and Speech Therapy.
- Continues on:
  - Propimex.
  - Whole Milk.
  - Prophree.
  - L-Carnitine.
  - Biotin.
  - Iron tablets.
  - Zofran PRN.

# Typical Presentation of Propionic Acidemia

# Non-specific Symptoms

- **Developmental delay with or without seizures**
- **Failure to thrive**
- **Chronic vomiting**
- **Hypotonia**
- **Recurrent infections**

# Acute Presentation

Most typically

- **Lethargy** progressing to coma
- **Poor feeding**
- **Abnormal muscle tone**
- Respiratory distress
- **Vomiting**

# Special features of PA

- Recurrent pancreatitis.
- Cardiomyopathy.
- Optic atrophy has been reported in a significant number of patients .
- Metabolic stroke involving basal ganglia may occur.

Cardiomyopathy:

Hypertrophic or Dilated.

No present evidence of relationship with metabolic control.

Serial echocardiographic surveillance.

Regular 1-2 year follow up in Emory Genetics clinic with cardiology.

# Neurologic Manifestations

- Metabolic Strokes.
- Severe developmental delays.
- Optic Atrophy.

## Management:

Optimal dietary control.

Other therapeutic interventions.

# Medical Management

Avoid fasting to prevent catabolism.

Limit amount of protein in diet.

Biotin as co-factor in diet.

G-tube placement for better handling of diet.

Regular Medical follow ups.

Cardiology Exams.

Ophthalmology Exams.

- Medical home with involvement of patient family and the healthcare provider.
- Involvement of pediatrician to make them knowledgeable about the disease.
- Carry Emergency Letter.
- Carry information about disease.

# Role of Antibiotics and Laxatives

- Antibiotics kills gut bacteria which are a source of propionic acid metabolites.
- Laxatives decrease the transition time in the gut which prevents bacteria from making any propionic acid metabolites.
- No clearly defined role presently, though it has been used in some patients during exacerbations.
- We have used lactulose in the past.

# Role of N-carbamylglutamate

- Study done by Dr Tuchman et al.
- Most patients with severe forms.
- Total number of patients was 7.
- Reduces Ammonia and Glutamine in Propionic Acidemia

# Liver transplant outcomes

- Natural protein intake increased.
- Anemia was corrected.
- Growth rate and mental development improved significantly.
- Good cognitive function.
- Reversal in cardiomyopathy in some patients.

# Monitoring Parameters

Acylcarnitine Profile

Total Carnitine Levels

Echocardiogram

EKG

CBC

CMP

## Null Mutations:

Nonsense mutations

Out-of-frame deletions and insertions.

Splicing mutations resulting in frameshift.

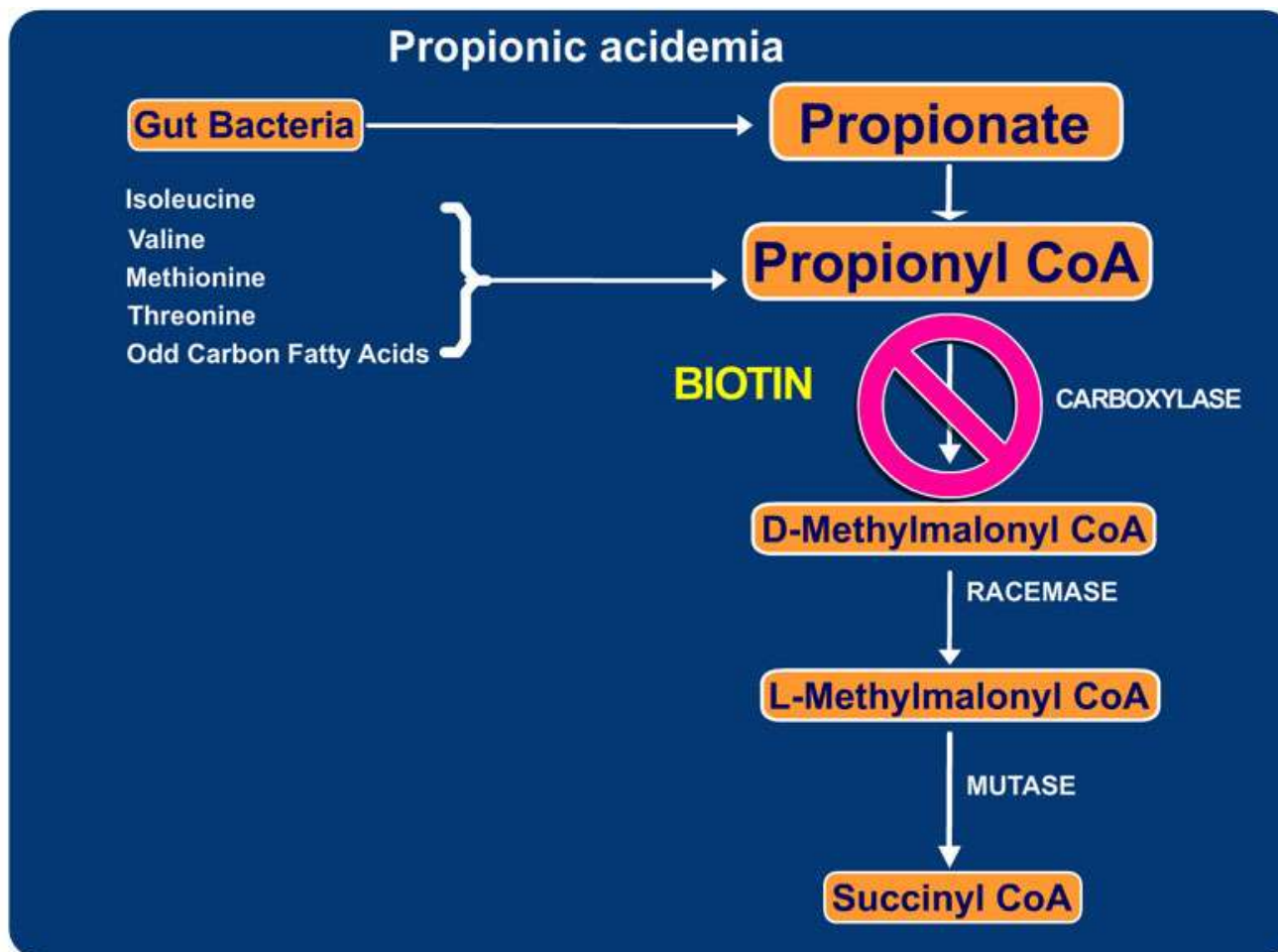
Missense Mutations which retaining partial activity.

Large deletion recently reported.

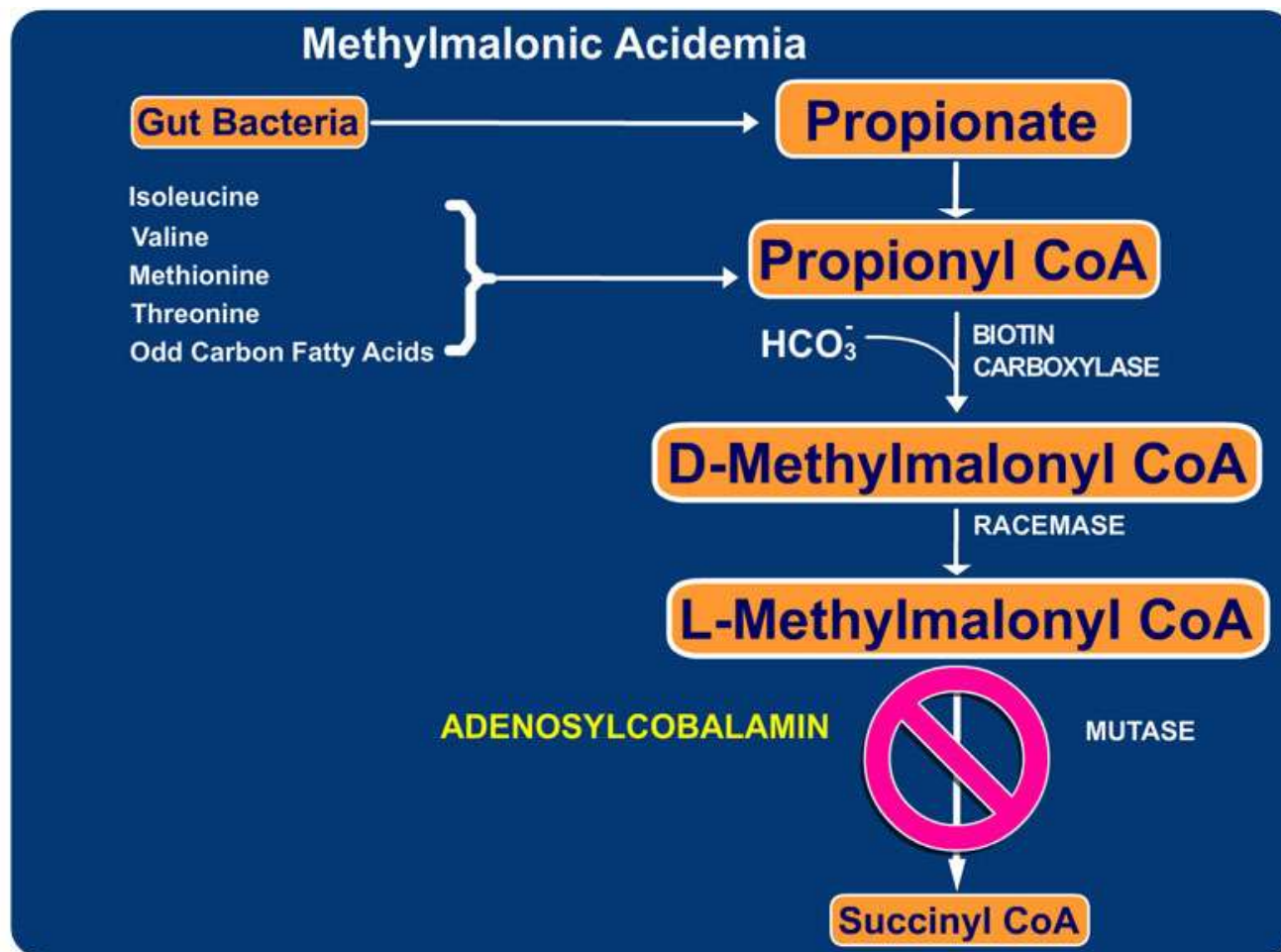
Exact phenotype depends on homozygous and functional hemizygous (with a second null allele) status.

Comparison to Methylmalonic Acidemia  
and other  
Cobalamin defects.

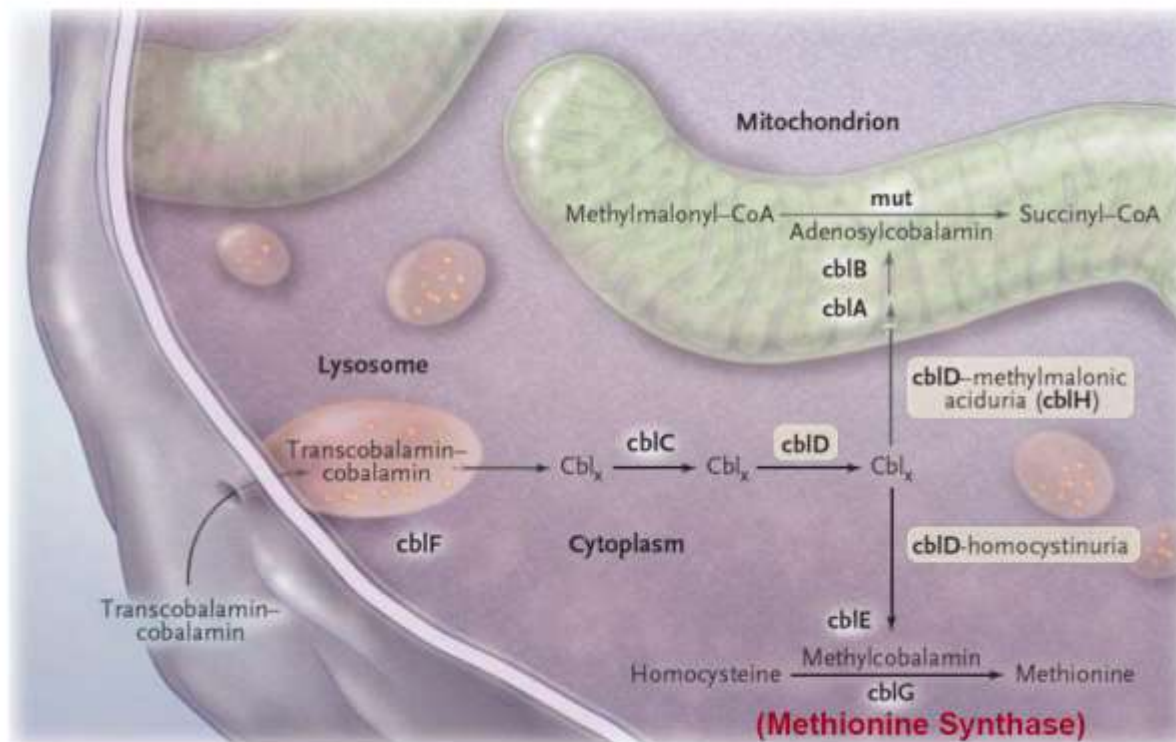
# Propionic Acidemia



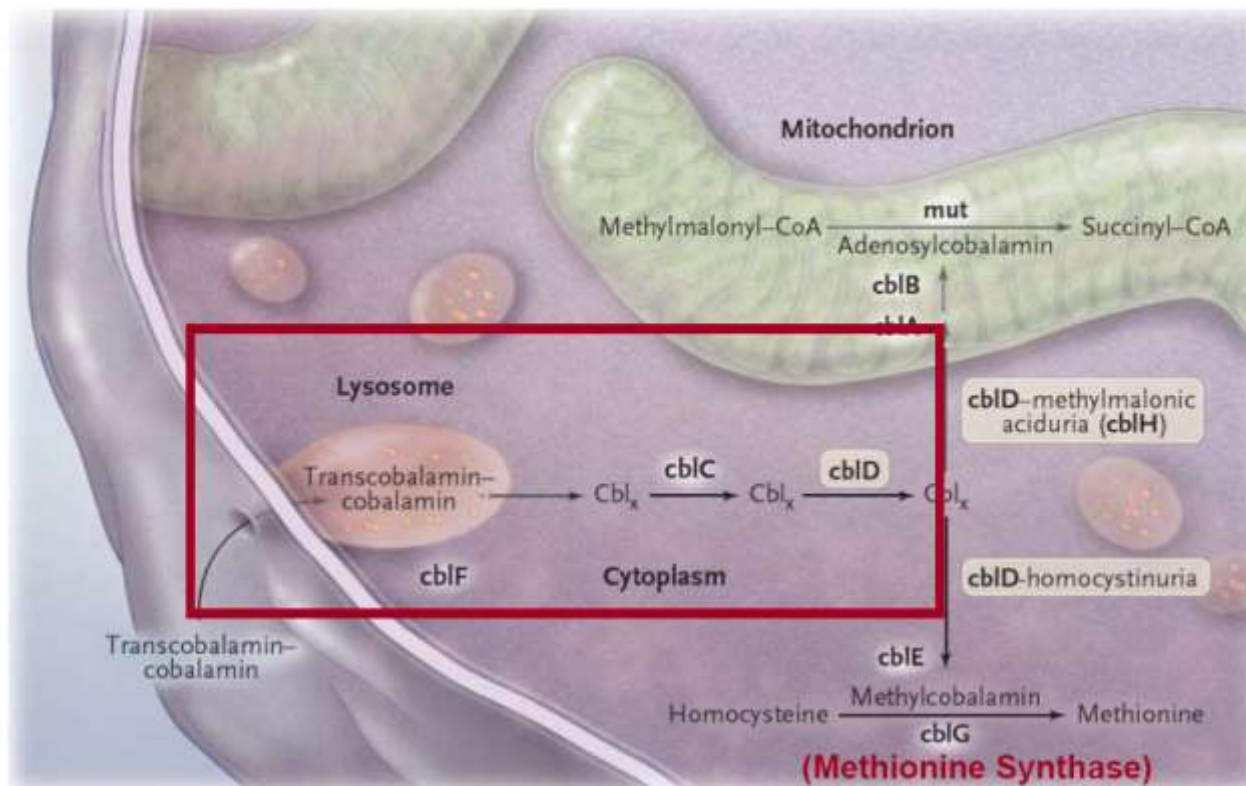
# Methylmalonic acidemia



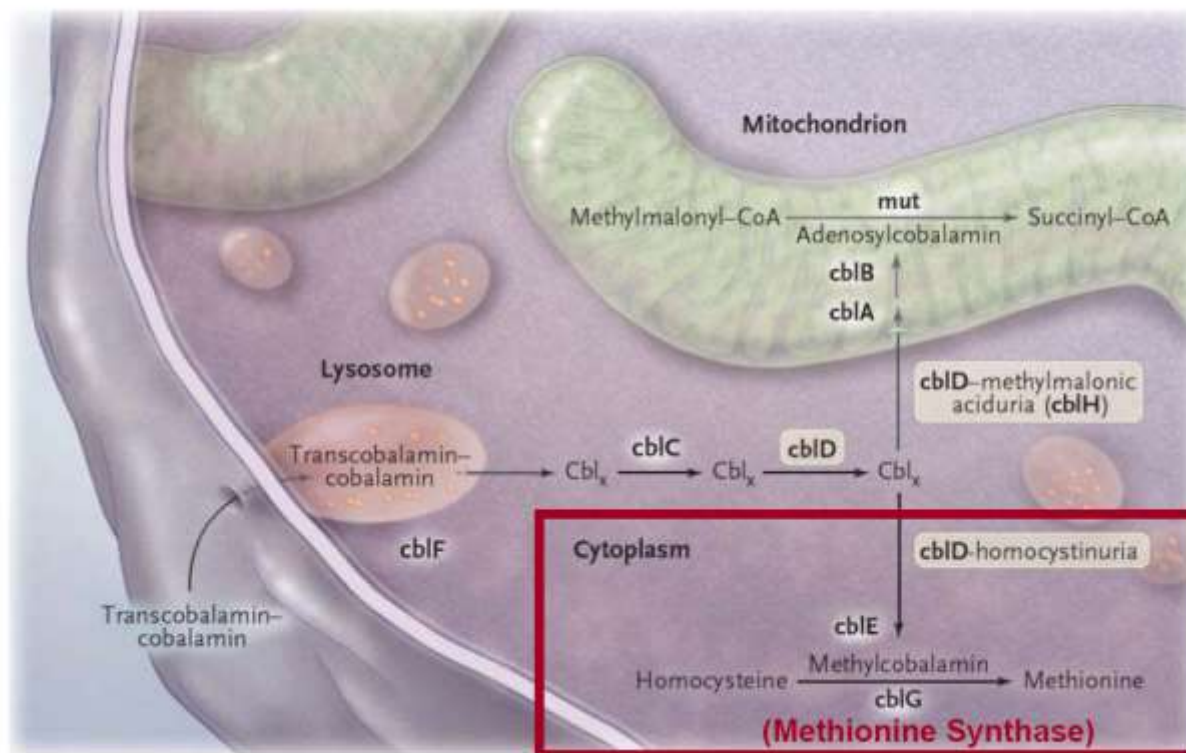
## Intracellular Cobalamin Metabolism



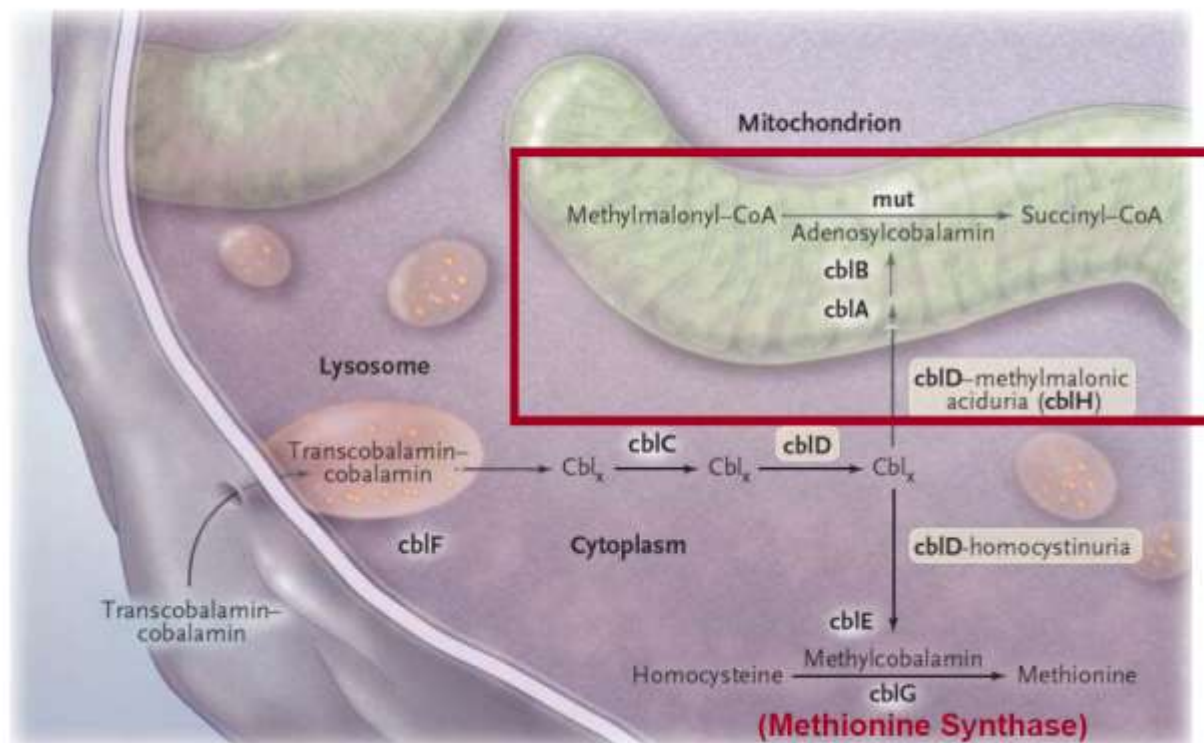
## Intracellular Cobalamin Metabolism



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## Intracellular Cobalamin Metabolism



- Adenosylcobalamin, an active form of vitamin B12, is a cofactor for the mutase enzyme.
- There are vitamin B12 responsive and non-responsive forms of MMA which are genetically distinct.
- Severe vitamin B12 deficiency as well as defects in processing and transport of vitamin B12 can give similar biochemical features.

# Special clinical features of methylmalonic acidemia

- Renal disease is a common late complication.
- Pancreatitis is a common complication.
- Metabolic “stroke” with subsequent choreoathetosis may occur.
- Optic atrophy may be late complication.
- Vitamin B12 responsiveness must be determined clinically.

# Treatment

- Treatment is similar to Propionic Acidemia.
- Dietary Modification.
- Avoidance of fasting.
- Hydro-oxycobalamin IM.
- Monitoring for renal function and CBC.
- Optimizing development by early intervention.

# Acknowledgements

Dr Rani Singh, PhD

Dr Paul Fernhoff, MD

Metabolic Genetics and Nutrition Clinic at Dept. of Human Genetics,  
Emory University School of Medicine.

Emory Newborn Screen follow up program.

Patients and their families.

Study	Pt. #	Lab Parameters	Pt outcomes
<a href="#">Saudubray JM</a> , Eur J Pediatr. 1999 Dec;158 Suppl 2:S65-9.	2	Ammonia Propionylcarnitine Ur. Methylcitrate	One died because of transplant complications. Second was healthy after 5 years.
<a href="#">Yorifuji T</a> , J Pediatr. 2000 Oct;137(4):572-4	1	Ammonia Propionylcarnitine Ur. Methylcitrate	Natural protein intake increased. Anemia was corrected. Growth rate and mental development improved significantly.
<a href="#">Morioka D</a> , Am J Transplant. 2005 Nov;5(11):2754-63	3	No specific test mentioned.	Post-transplant patient survival and recovery of the growth retardation were significantly better in the liver-oriented diseases.
<a href="#">Rela M</a> , Am J Transplant. 2007 Sep;7(9):2200-3	1	Normal Ammonia Stable	Normal growth. Acceptable neurological and psychomotor development.