The Urea Cycle Disorders – A Brief Review

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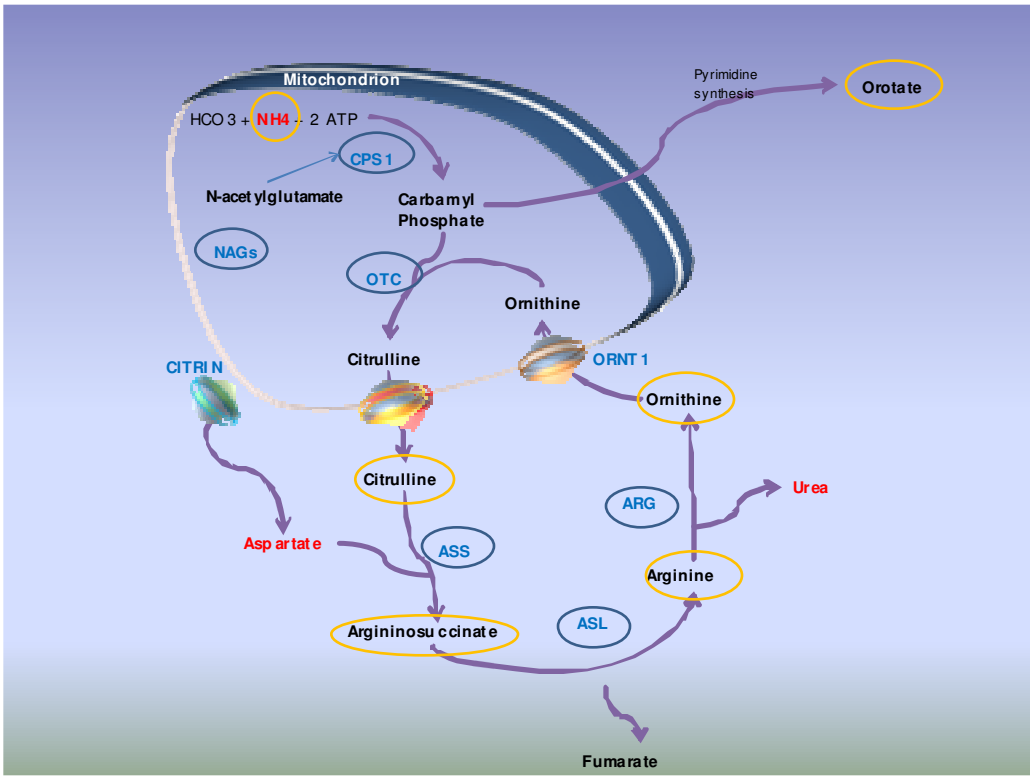
Introduction

- Urea cycle functions
  - trap toxic NH_3
  - de novo arginine synthesis
  - pH regulation by the liver (cycle consumes HCO_3)
- UCDs - 6 enzyme deficiencies , 2 transporter defects
- All present with hyperammonaemia
- 1 defect is X-linked (OTC) – most common – the rest are autosomal recessive
- Age of onset varies from 2 days to adulthood
- Severity varies from lethal hyperammonaemic encephalopathy to asymptomatic
- Combined incidence – estimated at around 1 in 8200 newborns – (1 for every 4 CF patients) – where are these patients?



Clinical presentations

- Severe deficiency of the 1st 4 enzymes, **CPSI, OTC, ASS, ASL** and the cofactor producer **NAGS** usually present as neonates
- Accelerated catabolism and liver immaturity accentuate decompensation
- Usually a normal delivery and discharge
- At home initial soft signs – refuse feeds, hypothermia, and somnolence
- Then rapidly develop lethargy; anorexia; hyperventilation, seizures; neurologic posturing and coma
- Imaging/post mortem – cerebral edema

- Mild/partial defects/female carriers of OTC - hyperammonaemia triggered by illness or stress
- First episode can occur all the way into adulthood
- LOA, cyclical vomiting, lethargy, psychosis
- Encephalopathic (slow-wave) EEG pattern
- Brain atrophy on MRI after repeated episodes
- ASL - chronic hepatic enlargement and elevation of transaminases

Clinical Presentations

- **ARG -** progressive spasticity, tremor, ataxia, growth failure – moderate hyperammonaemia – rare

- **ORNT1** – **HHH syndrome** (hyperornithinemia, hyperammonemia, homocitrullinuria) Intermittent moderate hyperammonemia , poor growth, intellectual impairment, spasticity and seizures common. Adults choose low-protein diet

- **CITRIN** deficiency – two phenotypes
- **Citrullinemia type II (CTLN2)** – adult sudden onset, recurrent hyperammonemia, neuropsychiatric Sx (delirium,irritability,delusions, flapping tremor,seizures, and coma. Death from brain edema.
  Steatosis and hepatofibrosis with normal LFTs
- **Neonatal Intrahepatic Cholestasis due to Citrin Deficiency (NICCD)** – mild transient cholestasis/steatosis/fibrosis – usually clears up in a year – some go on to develop CTLN2

Citrin deficiency is peculiar in that patients avoid carbohydrate

Lab Diagnosis

- **Plasma ammonia** – user defined routine wet analyser kits - Low threshold for ammonia screening
- **Plasma aminoacids**

1. High citrulline – distal defects – **ASS/Citrin>ASL>ARG**
2. Low - absent citrulline – proximal defects - **OTC/CPS1/NAGS**
3. Argininosuccinate - **ASL**
4. High Ornithine – **ORNT1**
5. High Arginine – **ARG**
6. High GLN, ASN, ALA – all UCDs – ammonia sump

- **Urinary Orotate** – high in all UCDs except CPS1 and NAGS therefore used to differentiate these from OTC
- **Pancreatic Secretory Trypsin Inhibitor - Citrin**

- **Confirmatory Tests**

Liver biopsy enzyme assay – NAGS,CPS, OTC
Biochem – ASS, ASL
Molecular - OTC

Differential for Hyperammonaemic Encephalopathy

Neonatal

- UCDs
- Organic Acidaemia's with CoA trapping – PA, MMA, GA, IVA, FAO's
- Transient Hyperammonaemia
- Liver Disease/ Hepatic Vascular Bypass (Infective/hypoxic)
- TPN

Older Kids/Adults

- All the above plus
- Milder UCDs, CITRIN, HHH, ARG
- Reye Syndrome
- Lysinuric Protein Intolerance
- Valproate
- UTI plus stasis with Urea Splitting Organisms

Acute management principals

1. Prevent protein catabolism – **dextrose** infusion, limit protein intake

2. Clear Ammonia – pump driven **dialysis** is fastest

3. Exploit Alternate pathways for Nitrogen Excretion

   Sodium Benzoate + glycine = hippurate
   Phenylbutyrate + glutamine = phenylacetylglytamine
   Arginine (not ARG)
   Citrulline - OTC/CPS/NAGS

Specific Management

- **Carglumic acid** (Carbaglu®,Orphan Europe) – activates CPS
  NAGS and CoA trapping Organic Acidaemias
- **Orthotopic Liver Transplant**
- **Liver Cell Transplant –** portal vein infusion of prepared hepatocytes – future drug?

Take Home Message

MEASURE AMMONIA MORE OFTEN

References

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