Clinical presentation in urea cycle disorders

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- Patients with urea-cycle disorders may present at almost any age

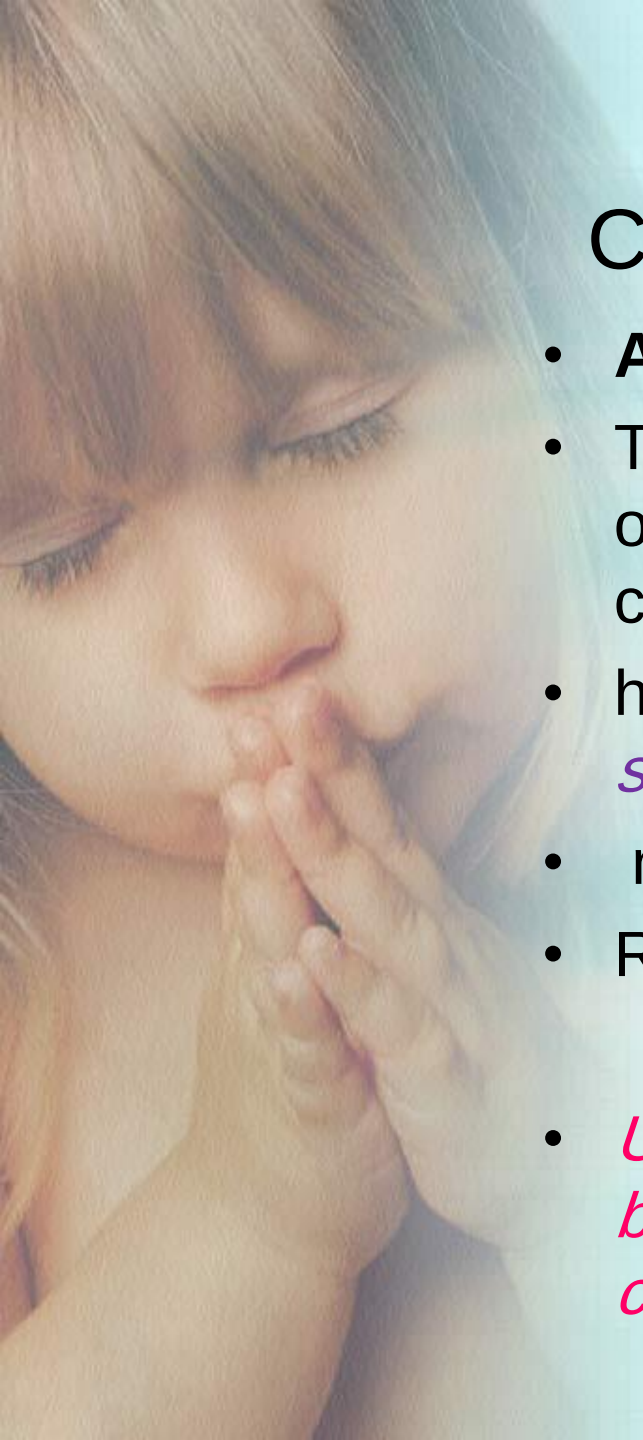
- Neonatal period
- Early infancy
- Puberty
- The patterns of the clinical presentation of hyperammonaemia are rather characteristic and are broadly similar for all the disorders except arginase deficiency

Neonatal presentation

- Most babies are initially healthy
- Common early symptoms are:
- Poor feeding
- Vomiting
- Lethargy and/or irritability
- Tachypnea ,transient mild respiratory alkalosis
- Sepsis like presentation
- Neurological and autonomic problems
- Most untreated babies will die or handicapped

Infantile presentation

- In infancy, the symptoms are generally rather less acute
- Anorexia
- vomiting and failure to thrive
- Hepatomegaly
- Symptoms similar to GI disorders
- developmental delay and behavioral problems
- Irritability ,lethargy
- more obvious encephalopathy with changes in consciousness level and neurological signs



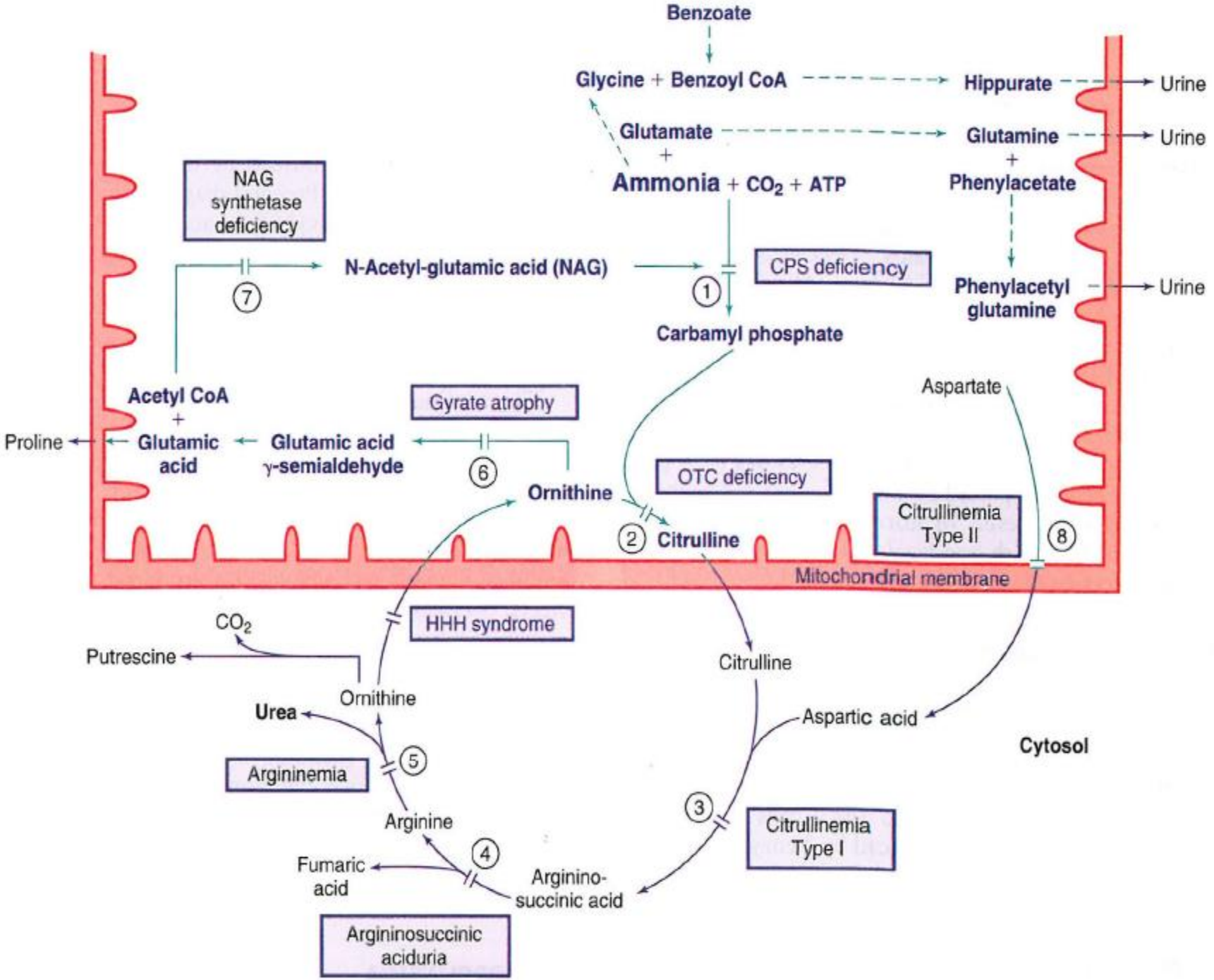
Children and adult presentation

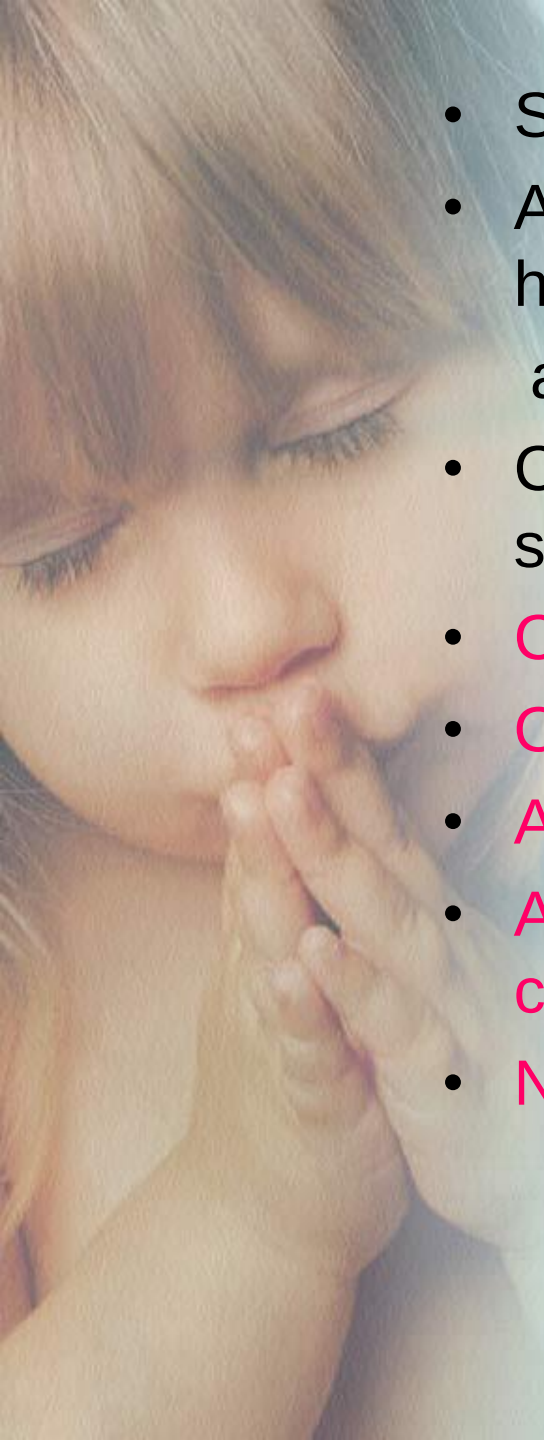
- **Acute encephalopathy**
- The patients first become anorexic, lethargic or agitated with behavior problems or confusion.
- headaches and vomiting *may be prominent, suggesting migraine or cyclical vomiting*.
- may be ataxic similar to *intoxicated*
- Reye like syndrome

- *Untreated, they continue to deteriorate, becoming comatose, and they may die. The cause of death is usually cerebral edema*

- **Chronic Neurological Illness**

- Learning difficulties
- mental retardation
- Patients may present with chronic ataxia, which is worse during intercurrent infections.


Benzoate
Glycine + Benzoyl CoA
Hippurate
Urine
Glutamate
+
Ammonia + CO_2 + ATP
Glutamine
Urine
+
Phenylacetate
NAG synthetase deficiency
N-Acetyl-glutamic acid (NAG)
CPS deficiency
Phenylacetyl glutamine
Urine
Carbamyl phosphate
Acetyl CoA
+
Glutamic acid
Gyrate atrophy
Proline
Glutamic acid γ-semialdehyde
Aspartate
Ornithine
OTC deficiency
Citrullinemia Type II
Citrulline
Mitochondrial membrane
CO_2
HHH syndrome
Putrescine
Ornithine
Citrulline
Urea
Aspartic acid
Cytosol
Argininemia
Arginine
Citrullinemia Type I
Fumaric acid
Arginino-succinic acid
Argininosuccinic aciduria



- Six enzyme defect cause urea cycle disorders
- All these defects are characterised by hyperammonaemia and disordered amino acid metabolism.
- Clinical presentation was similar but some specific presentation was described
- CPS: carbamylphosphate synthetase
- OTC: ornithine transcarbamylase
- ASL: argininosuccinate lyase
- ASS: argininosuccinate synthetase or citrolinemia type 1
- NAGS: N-acetyl glutamate synthetase

- CPS & NAGS

  most patient present in neonate periods
- OTC:

  More common form

  X linked dominant

  gall stone

  crystaluria or renal stone
- ASS :

  dry & brittle hair (trichorrhexis nodosa)

  crystaluria
- ASL :

  dry & brittle hair (trichorrhexis nodosa)

  gall stone
- Due to arginine deficiency

  Acrodermatitis eneteropathica

Arginase Deficiency

- Arginase deficiency commonly presents with spastic diplegia
- neurological abnormalities appear to be slowly progressive
- During the course of the disease, fits, ataxia and dystonia may develop.
- patients may present with an acute encephalopathy or anticonvulsant-resistant fits

Citrin Deficiency or citrullinemia II

- This disorder is a deficiency of the mitochondrial aspartate-glutamate carrier.
- The result is an intramitochondrial deficiency of aspartate
- The disorder presents at two ages: in the neonatal period with liver disease, cholestatic disorders
- in adulthood with neuropsychological symptoms

Hyperammonemia-Hyperornithinemia-Homocitrullinemia (HHH)

- Clinical manifestations of hyperammonemia may develop shortly after birth or may be delayed until adulthood.
- Progressive neurologic signs, such as lower limb weakness, increased deep tendon reflexes, spasticity, clonus, seizures, and varying degrees of psychomotor retardation
- No clinical ocular findings have been observed in these patients.

Transient Hyperammonemia of the Newborn

- In premature infants the upper limit of normal for blood ammonia may be as high as150 μmole/L. Blood levels approximate the adult normal values after a few weeks of life.
- Severe transient hyperammonemia has been observed in newborn infants. The majority of affected infants is premature and has mild respiratory distress syndrome. Hyperammonemic coma may develop within 2-3 days of life.

Thanks for your attention