Urea cycle disorders

Genetics

-Five catalytic enzymes: 1) CPS1 (Carbamoylphosphate synthetase I), 2) OTC (Ornithine transcarbamylase), 3) ASS1 (Argininosuccinic acid synthetase), 4) ASL (Argininosuccinic acid lyase), 5) ARG1 (Arginase-1)

-One cofactor-producing enzyme: NAGS (N-acetyl glutamate synthetase)

-Two amino acid transporters: 1) SLC25A15/ORNT1 (Ornithine translocase; ornithine/citrulline carrier), 2) SLC25A13/Citrin (aspartate/glutamate carrier)

Clinical findings/Dysmorphic features

1) NAGS deficiency: mimic of CPS1 deficiency (CPS1 inactive w/o N-acetylglutamate)

2) CPS1 deficiency: most severe UCD; rapidly develop hyperammonemia in newborn period

3) OTC deficiency (XLR): as severe as CPS1 deficiency; ~15% of carrier females develop hyperammonemia during lifetime, many require medical management of hyperammonemia

4) ASS1 deficiency: hyperammonemia also quite severe; individuals able to incorporate some waste nitrogen into UC intermediates

5) ASL deficiency: can present with rapid-onset hyperammonemia in newborn period; ASL past the point in UC at which all the waste N has been incorporated into the cycle --> chronic hepatic enlargement/elevation of transaminases; liver biopsy shows enlarged hepatocytes (fibrosis); trichorrhexis nodosa (responds to arginine supplementation)

6) ARG1 deficiency: no rapid-onset hyperammonemia; some present earlier with more severe sx; progressive spasticity, tremor, ataxia, choreoathetosis; late-onset hyperammonemia

7) ORNT1 deficiency (Hyperornithinemia-Hyperammonemia-Homocitrullinuria): variable onset (infancy to adulthood); chronic neurocognitive deficits, hyperammonemic crisis, chronic liver dysfunction

8) Citrin deficiency: can manifest in newborns as neonatal intrahepatic cholestasis (impaired release of bile from liver cells) --> bile builds up in liver --> impaired liver function

Etiology

-UCDs is estimated to be at least 1:35,000 births

-OTC deficiency 1:55,000; ASL deficiency 1:220,000; ASS1 deficiency 1:250,000; ARG1 deficiency 1: 950,000; CPS1 deficiency 1:1,300,000; NAGS deficiency 1:2,000,000

Pathogenesis

-NH3 is detoxificated to glutamine --> inc. glutamine synthesis in astrocytes --> cerebral edema

Genetic testing/diagnosis

1) Plasma NH3 of > 150 μmol/L (with nl anion gap and nl plasma glucose) --> strong ind. of UCD

2) PAA:

-Cit is product of proximal (CPS1, OTC, NAGS) and substrate for distal (ASS1, ASL, ARG1):

-CPS1-, NAGS-, OTC- and ORNT1-deficiency: Cit low/absent

-ASS1-deficiency: Cit markedly elevated

-Citrin deficiency: Cit moderate elevated + elevated threonine/serine ratio

-ASL deficiency: Cit moderate elevated + high argininosuccinic acid (ASA) in plasma/urine

-ARG1 deficiency: Cit normal + high arginine (may be reduced in all other UCDs)

-Plasma ornithine is elevated in ORNT1 deficiency, not elevated in OTC deficiency

-Urine homocitrulline is elevated ORNT1 deficiency

-Urine orotic acid: normal/low in CPS1 and NAGS deficiency and very high in OTC deficiency (carbamyl phosphate is shunted to pyrimidine synthesis resulting in high orotic acid)

-Urine orotic acid can also be increased in ARG1 deficiency and ASS1 deficiency