Phenylalanine Hydroxylase Deficiency

Genetics

-Gene: PAH (Phenylalanine hydroxylase; 12q23.2)

-AR

Clinical findings/Dysmorphic features

-Intolerance to essential amino acid phenylalanine

-Spectrum: most with severe PAH deficiency (classic PKU) develop profound and irreversible ID

-PHE levels above normal but below 1200 μmol/L (20 mg/dL) are at much lower risk for impaired cognitive development in the absence of treatment

-Clinical findings: epilepsy; ID and behavior problems including autistic features; Parkinson-like features; eczema; decreased skin and hair pigmentation

-Progressive white matter disease on brain MRI (90% of individuals with PAH deficiency)

-Musty body odor and mousy odor to urine (phenylacetic acid)

Etiology

-Frequency: 1:5,000 (Turkey, Ireland) to 1:10,000 (North European and East Asian)

Pathogenesis

-More than 900 different pathogenic variants in PAH have been identified to date

Genetic testing/diagnosis

-PAH deficiency detected by NBS in ~100%: presence of hyperphenylalaninemia using tandem mass spectrometry on a blood spot obtained from a heel stick

-Diagnosis established in a proband with:

1) Plasma PHE conc. persistently above 120 µmol/L (2 mg/dL) and altered Phe:Tyr-ratio (normal: <1; >3 is useful in the diagnosis of PAH deficiency) in untreated state with normal BH4 cofactor metabolism and/or

2) Finding of biallelic pathogenic variants in PAH by molecular genetic testing

-PAH: Seq 97-99%; InDel 1-3%

Others

-Treatment of classic PKU:

--> low-protein diet + PHE-free medical formula asap after birth (plasma PHE conc. of 120-360 µmol/L (2-6 mg/dL))

--> some benefit from adjuvant therapy with sapropterin (Kuvan, Tetrahydrobiopterin/BH4)

--> large neutral amino acid (LNAA) compete with PHE at blood brain barrier

-Tetrahydrobiopterin (BH4) deficiency: hyperphenylalaninemia from impaired synthesis/ recycling of BH4 (cofactor in the PHE, TYR, TRP hydroxylation reactions)

-Maternal PKU/PAH Deficiency: ID (90%), microcephaly (70%), CHD (12%), IUGR --> maternal PHE conc. of 120-360 µmol/L during pregnancy is recommended