Tyrosinemia type I

Genetics

-Gene: FAH (fumarylacetoacetase)

-AR

Clinical findings/Dysmorphic features

-Untreated: young infants with severe liver involvement or later in first year with liver dysfunction and renal tubular dysfunction, growth failure and rickets; repeated, often unrecognized, neurologic crises (1-7days) --> change in mental status, abdominal pain, peripheral neuropathy, and/or respiratory failure; death < 10y, typically from liver failure, neurologic crisis, or hepatocellular carcinoma

Etiology

-1 in 100,000; in general US population, carrier frequency is estimated at 1:100 to 1:150

Pathogenesis

-FAH is terminal enzyme in the tyrosine catabolic pathway; fumarylacetoacetate (FAA) is immediate precursor:

--> accumulates in hepatocytes, causing cellular damage and apoptosis

--> is diverted into succinylacetoacetate and succinylacetone

--> succinylacetone interferes with activity of 2 major hepatic enzymes:

1) parahydroxyphenylpyruvic acid dioxygenase (p-HPPD) --> elevation of plasma tyrosine

2) PBG synthase --> reduced activity of the enzyme δ-ALA dehydratase; reduced heme synthesis; increased δ-aminolevulinic acid (δ-ALA; induces acute neurologic episodes; increased urinary excretion of δ-ALA (see AIP))

Genetic testing/diagnosis

-NBS: presence of succinylacetone (MS/MS): pathognomonic for tyrosinemia type 1

-Supportive findings: increased succinylacetone in blood and excretion in urine; elevated plasma concentration of tyrosine, methionine, phenylalanine

-FAH seq: >95%, In/Del: unknown; targeted p.Pro261Leu first in AJ (> 99% of pathogenic variants in this population); c.1062+5G>A (IVS12+5 G>A) accounts for 87.9% of variants in French-Canadian population; 4 FAH variants (c.1062+5G>A (IVS12+5 G>A), c.554-1G>T (IVS6-1 G>T), c.607-6T>G (IVS7-6 T>G), p.Pro261Leu) account for ~60% of variants in US population

Others

-Treatment:

1) Nitisinone/NTBC (blocks p-HPPD; second step in the tyrosine degradation pathway) --> prevents accumulation of fumarylacetoacetate and its conversion to succinylacetone

2) Low-tyrosine diet --> > 90% survival rate, normal growth, improved liver function, prevention of cirrhosis, correction of renal tubular acidosis, improvement in secondary rickets