# Tyrosinemia Hepato-gastrointestinal manifestations

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# Hereditary Tyrosinemia Type 1

- Hereditary tyrosinemia type 1 (HT1), also known as **hepatorenal tyrosinemia**, is the **most severe** disorder of tyrosine metabolism.
- HT1 occurs in 1 in 12,000 to 1 in 100,000 individuals of Northern European descent.
- HT1 is caused by deficiency of **fumarylacetoacetate hydrolase** (FAH), the last enzyme in the pathway of tyrosine catabolism.
- The mutagenicity of FAA is thought to be the cause of the high rate of HCC in HT1.
- Tyrosine itself is not toxic to the liver or kidney but causes **dermatologic**, **ophthalmologic**, and possibly **neurodevelopmental** problems.

# Hereditary Tyrosinemia Type 1

- Several inborn errors of metabolism present with cholestasis during the neonatal period including tyrosinemia is important because specific treatment is available.
- As a treatable disorder it requires promp diagnosis to initiate effective therapy.
- FAA has a short intracellular half-life and thus is not found in body fluids of HT1 patients.
- The principal metabolites of FAA, **succinylacetoacetate** and **succinylacetone** , are released into the circulation and can be measured for diagnosis.

# Introduction

- HT1 is characterized by severe, progressive liver disease and renal tubular dysfunction.
- The latter typically is manifest as the Fanconi syndrome with renal tubular acidosis, aminoaciduria, and hypophosphatemia (due to phosphate wasting) .
- Features of rickets often are present in untreated patients. Patients not diagnosed by newborn screening typically present in early infancy with failure to thrive and hepatomegaly.
- Some develop conjugated hyperbilirubinemia. An often marked elevation in serum alpha fetoprotein (AFP) is common in HT1.
- Studies in newborns have shown that cord blood AFP is elevated at a time when tyrosine levels are still normal .
- This observation suggests that the liver disease begins prenatally, as does the common finding of nodularity or cirrhosis in affected neonates.

# Clinical Features

- Progression of the liver disease can be chronic or acute, with rapid deterioration and early death.
- Hypoglycemia and coagulation abnormalities
- Serum aminotransferase levels typically are only **mildly elevated** and often disproportionately low compared with the marked degree of coagulopathy
- Complications of liver failure, including jaundice, ascites, and hemorrhage, often develop
- The chronic form consists of a mixed micronodular and macronodular cirrhosis
- The risk of developing **HCC** is high in untreated survivors, occurring in as many as **37%** of untreated patients older than two years of age

# Clinical Features

- Severe neurologic manifestations are common in poorly controlled HT1 and contribute to morbidity and mortality.
  - Neurologic crises resembling the crises of the neuropathic porphyrias
  - Acute episodes of peripheral neuropathy were characterized by severe pain with extensor hypertonia , vomiting or paralytic ileus , muscle weakness , and self-mutilation .
  - Required mechanical ventilation because of paralysis
  - Intellectual disability is not a feature

# Clinical Features

- Approximately 30% of patients display **cardiomyopathy** at the time of diagnosis, with interventricular septal hypertrophy being the most common finding.
- This disease manifestation is **reversible** with nitisinone therapy.

# Liver involvement

- Undetected or untreated children presenting before age six months typically have acute liver failure with initial loss of synthetic function for clotting factors.
- PT and PTT are markedly prolonged and not corrected by vitamin K supplementation; factor II, VII, IX, XI, and XII levels are decreased; factor V and factor VIII levels are preserved.
- Progression of the liver disease can be chronic or acute, with rapid deterioration and early death .
- Liver dysfunction commonly results in hypoglycemia and coagulation abnormalities.
- Serum aminotransferase levels typically are only mildly elevated and often disproportionately low compared with the marked degree of coagulopathy.

# Liver involvement

- Complications of liver failure, including jaundice, ascites, and hemorrhage, often develop.
- Paradoxically, serum transaminase levels may be only modestly elevated; serum bilirubin concentration may be normal or only slightly elevated, in contrast to most forms of severe liver disease in which marked elevation of transaminases and serum bilirubin concentration occur **concomitantly** with prolongation of PT and PTT.
- Resistance of affected liver cells to cell death may explain the observed discrepancy in liver function.

# Liver involvement

- This early phase can progress to liver failure with ascites, jaundice, and gastrointestinal bleeding.
- Children may have a characteristic odor of "boiled cabbage" or "rotten mushrooms." Infants occasionally have persistent hypoglycemia; some have hyperinsulinism .
- Others have chronic low-grade acidosis. Untreated affected infants may die from liver failure within weeks or months of first symptoms

# Hepatocellular carcinoma

- The chronic form consists of a mixed micronodular and macronodular cirrhosis.
- The risk of developing hepatocellular carcinoma is high in untreated survivors, occurring in as many as 37 percent of untreated patients older than two years of age .
- Cancer formation is thought to be caused by the mutagenicity of FAA.
- Both the acute and chronic forms can occur in affected siblings or other patients with identical genotypes .
- Those children who are not treated with nitisinone and a low-tyrosine diet and who survive the acute onset of liver failure are at high risk of developing and succumbing to hepatocellular carcinoma.

# Hepatocellular carcinoma

- Intrafamilial variability in the severity of HT1 may be caused in part by somatic mosaicism. Immunohistologic analysis of liver in some patients shows FAH enzyme activity in some regenerating nodules .
- In these areas of regeneration, one of the mutant alleles has reverted spontaneously to the normal genotype. Reversion to the normal allele in some individuals may be associated with milder liver disease, but the risk for liver cancer remains .

# Hepatocellular carcinoma

- If untreated, patients with HT1 have a significantly shortened lifespan.
- Patients may die of acute liver failure before the second year after birth or from chronic liver failure or hepatocellular carcinoma before the end of the second decade.

# Liver Transplantation

- OLT is performed in patients with persistent liver failure who do not respond to Nitisinone therapy or have hepatic malignancy .
- In one series of eight patients transplanted at a median age of 64 months, plasma tyrosine and AFP returned to normal, urinary SA decreased, and, if present, hypertrophic cardiomyopathy resolved .
- Renal tubular function remains abnormal in many transplanted patients, and careful monitoring of kidney function is therefore recommended .
- Plasma and urinary SA levels are not completely normalized after transplantation , but the clinical significance of this fnding is unknown.
- OLT is not predicted to prevent the accumulation of mutagenic and toxic FAA in renal tubules. More extensive long-term studies are needed to determine whether renal pathology (progressive tubular disease or renal cancer) can be prevented by OLT in the absence of Nitisinone treatment.

# Thanks for your attention