
In the name
of God...

Tyrosinemia

Dr. Hossein Moravej

Associate P{rofessor of Pediatric Endocrinology and Metabolism

Shiraz University of Medical Sciences

When should we suspect tyrosinemia type 1?

Tyrosinemia type 1 ?

Newborn screening

Symptomatic patients

Symptomatic 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.
- Progression of the liver disease can be chronic or acute, with rapid deterioration and early death.

Symptomatic patients

- 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.
- Complications of liver failure, including jaundice, ascites, and hemorrhage, often develop.

Symptomatic patients

- 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.

Symptomatic patients, Kidney

- Renal tubular dysfunction.
- The latter typically is manifest as the Fanconi syndrome with renal tubular acidosis, aminoaciduria, and hypophosphatemia.
- Features of rickets often are present in untreated patients.

Symptomatic patients, Neurology

- Severe neurologic manifestations are common in poorly controlled HT1 and contribute to morbidity and mortality.
- In one study of 48 children with tyrosinemia identified with neonatal screening, neurologic crises resembling the crises of the neuropathic porphyrias occurred in 20 (42 percent)

Symptomatic patients, Neurology

- Acute episodes of peripheral neuropathy were characterized by severe pain with extensor hypertonia (75 percent), vomiting or paralytic ileus (69 percent), muscle weakness (29 percent), and self-mutilation (8 percent). Eight children required mechanical ventilation because of paralysis.
- Between crises, most patients regain normal function.
- Intellectual disability is not a feature.

Symptomatic patients, Heart

- Approximately 30 percent 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.

Symptomatic patients

- 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.


DIAGNOSIS
shutterstock.com · 1706113012

Newborn screening

- High tyrosine or methionine level:

  Transient tyrosinemia of the newborn, tyrosinemia type I or II or

  III, or other liver diseases.

- Succinyl acetone level in blood (?)
- Many newborn screening programs perform sensitive SA measurements on dried blood spots

Newborn screening

- Plasma tyrosine concentration in affected infants can be normal in cord blood and during the newborn period.
- Elevated plasma tyrosine concentration can also be a nonspecific indicator of liver damage or immaturity; for example, in infants taking a high-protein formula

Screening confirmation, or symptomatic disease

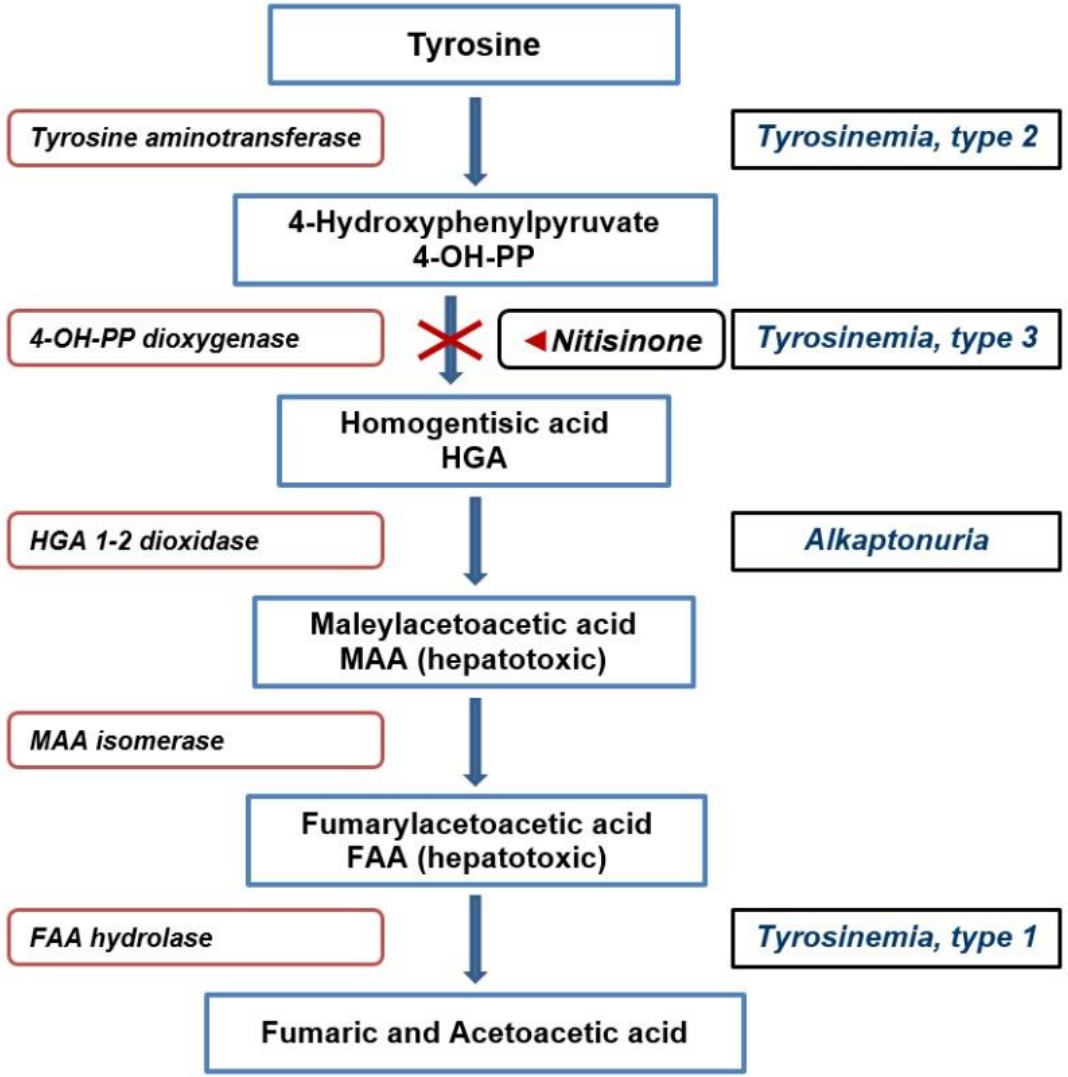
- LFT, PT,INR, PTT, AFP
- Plasma aminoacids: high tyrosine. Methionine and phenylalanine levels
- Serum or urine SA: high
- Urine organic acids: Elevated urinary concentration of tyrosine metabolites **4-hydroxyphenylpyruvate, 4-hydroxyphenyllactate, and 4-hydroxyphenylacetate** detected on urine organic acid testing
- Increased urinary excretion of the compound δ-ALA

Symptomatic patients

- An individual with liver disease and normal serum concentration of AFP and normal PT/PTT has a low probability of having tyrosinemia type I.


MANAGEMENT
TRAINING
SKILLS
EMOTIONAL
COMMITMENT
INNOVATION
TEAM
LEADERSHIP
MISSION
RISK
CONDUCT
STRENGTH
MOTIVATION
TRUST
ABILITY
COMMERCE

- Treatment of choice: Nitisinone, (NTBC) which inhibits 4-OH phenylpyruvate dioxygenase (HPD).



Nitisinone

- Nitisinone should be started as early as possible (ie, immediately after diagnosis of HT1 by blood or urine measurement of SA).
- Nitisinone increases blood tyrosine levels
- Restriction of protein intake is needed to prevent the side effects of elevated blood tyrosine levels.

Nitisinone

- Many patients on the combination of nitisinone therapy and protein restriction develop low blood phenylalanine levels, which is linked to neurodevelopmental problems.
- Phenylalanine supplementation is used in these patients to achieve normal blood levels.

Efficacy of Nitisinone

Efficacy of Nitisinone

- Most patients improve clinically.
- If starts at an early age, reduces the risk of early development of hepatocellular carcinoma.
- Decreases the need for orthotopic liver transplantation (OLT), particularly when started in early infancy.

Efficacy of Nitisinone

- The long-term risk of developing neurologic problems on nitisinone therapy is unknown.
- Some studies have documented a higher incidence of behavioral problems or cognitive impairment even in patients treated from early infancy.
- It is not known whether this phenotype is related to elevated tyrosine, **phenylalanine deficiency**, or caused by other factors. However, low phenylalanine levels are of particular concern in this regard.
-

Dose of Nitisinone

- Starting dose: 1 mg/kg per day, po, in one or two doses.
- Dietary protein intake is varied to keep the plasma tyrosine level 200 to 600 micromol/L.
- If the biochemical parameters (except plasma SA) have not normalized within one month of starting therapy, the dose should be increased to 1.5 mg/kg/day.
- Maximum dose is 2 mg/kg/day.

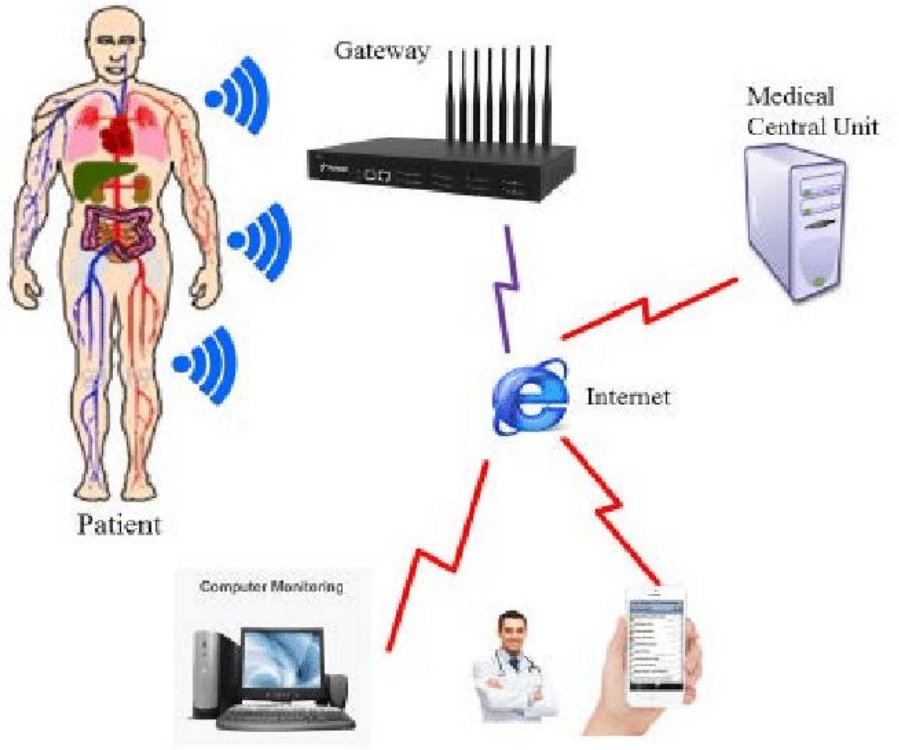
Dose of Nitisinone

- The dose of nitisinone should be adjusted to completely suppress excretion of SA.
- However, it may take as long as three months for complete suppression of SA to occur.
- In older individuals, therapeutic blood levels of nitisinone can often be achieved with doses <1 mg/kg/day.

Dose of Nitisinone

- Monitoring of the nitisinone blood levels is recommended for dose adjustment and also to check therapy compliance.
- A general target for blood level of nitisinone is 40 to 60 micromol/L.

Monitoring


Gateway
Medical
Central Unit
Internet
Patient
Computer Monitoring

Metabolic monitoring

- Monthly for the first year,
- Every three months until age five years
- Every six months thereafter.

Metabolic monitoring

- Plasma amino acids (especially tyrosine and phenylalanine),
- blood or urinary SA
- liver and kidney function tests,
- (CBC) with differential (leukopenia, thrombocytopenia)
- Nitisinone levels
- Serum AFP (which increases further with hepatocellular carcinoma).
-

Alpha fetoprotein

- Serum AFP can take many months to normalize after nitisinone therapy is started. Trend of the decline, should be continuously downward.
- In one study, AFP levels did not normalize in approximately one-third of patients, even after one year of nitisinone treatment.
- If AFP level begins to increase, an evaluation of possible hepatocarcinoma should be initiated.

Monitoring

- Ophthalmologic examination; annually
- Hepatic imaging (magnetic resonance imaging is preferred); annually

- Supplementation of phenylalanine in the diet is suggested when two independent measurements show phenylalanine levels of <30 micromoles/L.

Liver transplantation

Indications:

- Persistent liver failure who do not respond to nitisinone therapy
- Hepatic malignancy

Liver transplantation

- plasma tyrosine returns to normal.
- AFP returns to normal.
- SA decreases, but not completely normalized.
- Hypertrophic cardiomyopathy resolves. clinical significance of this finding is unknown.
-

Liver transplantation

- Renal tubular function may remain abnormal, careful monitoring of kidney function is recommended.
- **More extensive long-term studies** are needed to determine whether renal pathology (progressive tubular disease or renal cancer) can be prevented by LT in the absence of nitisinone treatment.

THANK YOU
for your
ATTENTION!