Radiologist and Management of Hepatic Involvement in Hereditary Tyrosinemia Type 1

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ALGIERS
Hereditary tyrosinemia type 1 (HT1) is an autosomal recessive amino acid disorder.

It is rare (1/100000 births) except in Finland and in Quebec.

According to “the Algerian Association of rare disease” (ADEM ) there are nationally, 50 to 60 children affected, the eldest is 14 years old.

It occurs due to a deficiency of fumarylacetoacetate hydrolase (FAH), which is a terminal enzyme in Tyrosine metabolism.
Clinical presentation:

Severe liver dysfunction leading to cirrhosis, liver failure, portal hypertension & HCC

Renal tubular dysfunction & Rickets

Growth failure

Acute Neurologic crisis
Déficit en FAH

Accumulation of FAA in the hépatocytes

Metabolised to succinyl-acéto-acétate & succinyl-acétone

Interferes with hepatic enzymes activity such as:

- PBG synthase
- p-HPPD

Hepatic injury leading to apoptosis

Heme decreased synthesis

Phenyl -ALA []

Decreased qctivity of δ-ALA déshydratase (liver – hématies)

++ Blood & urine

Increased [ ] tyrosine

Phenyl -ALA []
Oncogenesis

Ongoing hepatocyte injury from accumulation of FAA results in increased liver cell turnover

Leading to the formation of regenerative nodules

Within regenerative nodules, some hepatocytes can undergo further genomic changes with atypia and hence progress to liver cell dysplasia.

Nodules increase in size and cellularity, giving rise to the formation of dysplastic nodules and, finally, HCC
Biochemical Findings:

- **In blood**: increased concentration of succinylacetone, tyrosine, methionine, and phenylalanine
- **In Urine**: elevated concentration of succinyl choline, tyrosine metabolites, and the compound δ-ALA.

Molecular genetic testing:

- molecular genetic testing identification of biallelic pathogenic variants in FAH
Management / Treatment

Nitisinone (Orfadin®):

Blocks parahydroxyphenylpyruvic acid dioxygenase (p-HPPD), the second step in the tyrosine degradation pathway, and prevents the accumulation of FAA and its conversion to succinylacetone.

Low tyrosine diet.

Nitisinone increases blood concentration of tyrosine, necessitating a low-tyrosine diet to prevent tyrosine crystals from forming in the cornea.

Liver Transplantation: Only Definitive Treatment
RADIOLOGIST AND MANAGEMENT OF TYROSINEMIA TYPE 1

« As clinically indicated »
Biopsy! is **NOT** indicated in the Diagnosis of **HCC**!

The main imaging challenge is to distinguish Regenerative, Siderotic & Low Grade Dysplastic Nodules from small **HCC**.
Imaging Modalities

Doppler-Ultrasonography:

First-line examination to detect liver lesions

Technique:

Doppler

B mode: 5-7 Mhz probe
High frequency linear probe
MRI

Modality of choice, important for the assessment of cirrhosis and its complications.

Faster sequences now allow high-quality liver imaging

Automated contrast detection methods with faster sequences allow capture of the arterial phase, essential for the detection of HCC.

The lack of Ionizing Radiation permits routine use of MRI screening.
Protocol

Scout/ Coronal T2 HASTE
Axial T2 SE et STIR
Axial T1 In/Opposed phase
Axiale DWI ( B 0 - 50 - 400 - 1000 )
Axiale VIBE:
- Basal
- Arterial phase
- Portal phase
- Late phase 3 mn
FINDINGS
US

- Irregular Surface (nodularity)
- Overall Coarse and Heterogeneous Parenchyma
- Hepatic Dysmorphia
- Periportal Thickening (fibrosis)
Dysmorphie hépatique:

- Irregular contours
- Hypertrophy of Seg I / Atrophy of Seg IV
- Hepatic dysmorphia
Coarse heterogeneous echotexture

Periportal Thickening
Signs of Portal Hypertension:

Doppler flow changes

- Enlarged portal vein: >13 mm
- Slow portal venous flow <15 cm/sec
- Reversal or to-and-fro portal venous flow
- Portal venous thrombosis +/- cavernous transformation
- Enlarged SMV and splenic vein: >10 mm
- Portosystemic collaterals
- Portalisation of hepatic vein waveform

Splenomegaly
Ascites
Portal hypertension Signs

- Enlarged portal vein
- Splenomegaly
MRI findings include morphologic changes (same as on CT and US)

MRI has a significant role in screening cirrhotic livers for small HCCs
No nodular enhancement in arterial phase
Chronic Hepatopathy: Irregular Contours, Heterogeneous Signal
No nodular enhancement in arterial phase
Chronic hepatopathy
NODULES

Regenerative Nodules (or Siderotic)

Dysplastic Nodules

Hepatocellular Carcinoma
Regenerative & Siderotic Nodules

T1: variable: Usu. Iso Occa: Hyper Intense
T2: Isointense hypointense if siderotic
Regenerative nodules (or cirrhotic nodules)

T1 + Gado: No early enhancement and washout
As most Supply is from the Portal vein
Regeneratives nodules isointense on T2
Siderotic nodule, hypointense on T2
Dysplastic Nodule

May be of Low or High grade, and thus have variable appearances:

**Low-grade** nodules will resemble regenerative nodules

**High-grade** nodules will resemble HCCs
Hepatocellular Carcinoma (HCC)

T1 C+ (Gd):
- Arterial phase enhancement and washout
- Late enhancing capsule
- Growth in the interval between studies

T2:
- Typically mildly or moderately hyperintense

MR angiography may also be used to assess portal vein patency and portosystemic collaterals.
Segment 2 nodule: Hypointense nodule on fast T1 with fat Sat

Arterial phase enhancement and washout (e)

Late enhancing capsule (f).
DWI in phase:
- hypo signal T1 (a)
- typical Hypersignal T2
Tyrosinemia is a very rare metabolic disease but should not be ignored as it can result in hepatic and renal failure.

Since biopsy is not conducted, MRI plays a crucial role in diagnosing hepatocellular carcinoma.

Transplantation is the best available treatment for tyrosinemia in cases of advanced cirrhosis and hepatic failure with or without Hepatocellular carcinoma.
THANK YOU
References


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