NON-CIRRHOTIC PORTAL HYPERTENSION

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- Portal HTN: clinical syndrome defined by a portal venous pressure gradient between the portal vein and inferior vena cava exceeding 5-6 mmHg

- Cirrhosis is the most common cause of portal hypertension, but portal hypertension can also be present in the absence of cirrhosis, a condition referred to as "noncirrhotic portal hypertension."

- NCPH: heterogeneous group of liver disorders of vascular origin, leading to PHT with near normal HVPG.

- Portal hypertension develops when there is resistance to portal blood flow and is aggravated by increased portal collateral blood flow

- Resistance most often occurs within the liver, prehepatic or posthepatic

- Increased resistance:

Structural changes occur when there is distortion of the liver microcirculation by fibrosis, nodules, angiogenesis, and vascular occlusion.

Dynamic changes (due to increased vasoconstrictors) occur when there is contraction of activated hepatic stellate cells and myofibroblasts that surround hepatic sinusoids and are in the fibrous septa and vascular smooth muscle cells of the hepatic vasculature.

PH

- Western countries:

Cirrhosis most common

Non-cirrhotic < 10 %

- Worldwide

Non-cirrhotic: Schistosomiasis, portal vein thrombosis, idiopathic

- Often asymptomatic until complications develop

Complications of portal hypertension include:

- Variceal hemorrhage
- Portal hypertensive gastropathy
- Ascites
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome
- Hepatic hydrothorax
- Hepatopulmonary syndrome
- Portopulmonary hypertension
- Cardiomyopathy

HVPG

- HVPG = WHPG – FHVP
- [wedged hepatic venous pressure (WHVP, which reflects portal venous pressure minus free hepatic venous pressure (FHVP, which reflects intra-abdominal pressure)]
- obtained by hepatic vein catheterization.
- FHVP is determined by direct measurement of pressure in the hepatic vein.
- WHVP is typically obtained by balloon occlusion of the hepatic vein, though it can also be estimated by wedging the catheter in the end tributaries of a hepatic vein.

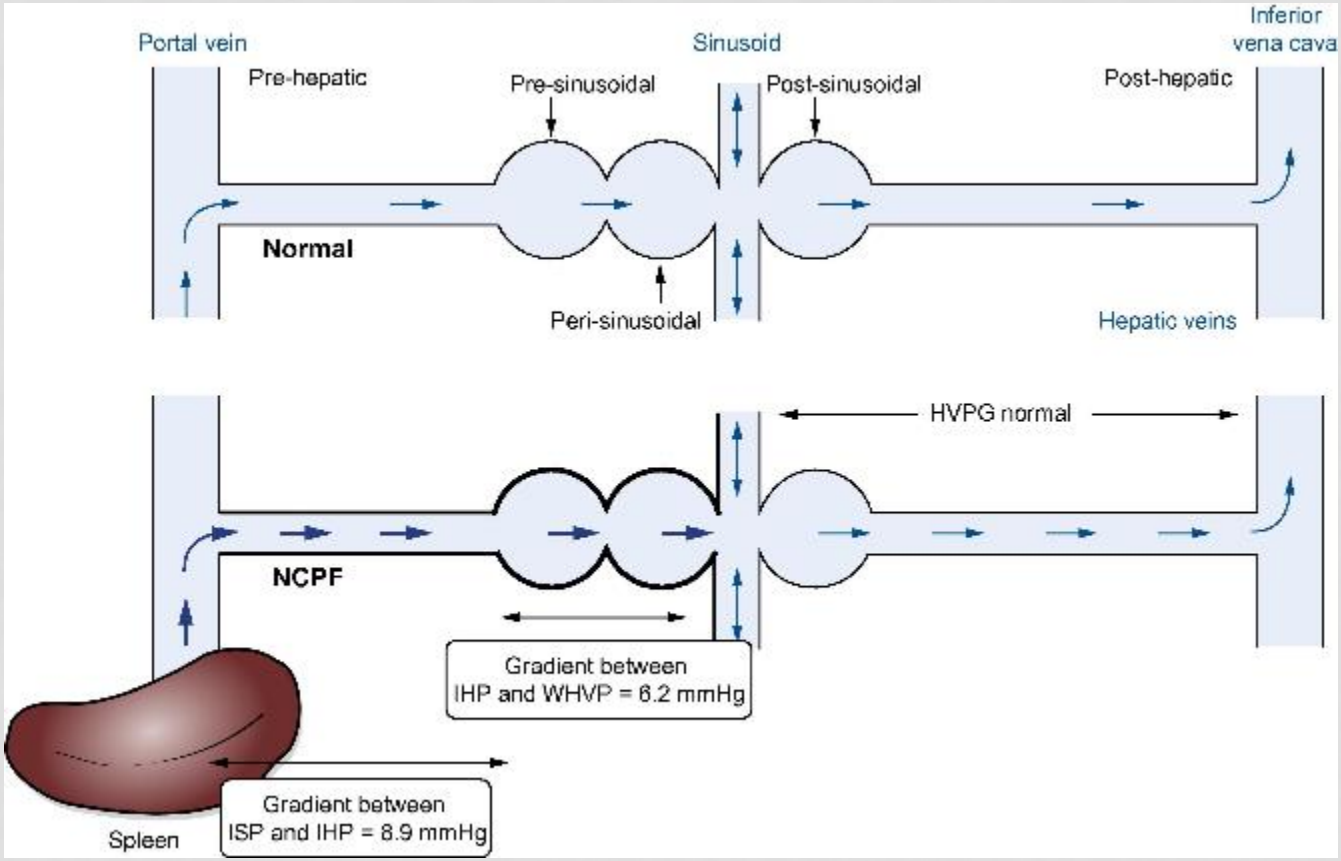
IMPLICATIONS OF HVPG

In patients with **compensated** disease:

- HVPG 10 mmHg: Development of gastroesophageal varices, development of hepatocellular carcinoma, decompensation after surgery for hepatocellular carcinoma
- HVPG 12 mmHg: Variceal bleeding
- HVPG 16 mmHg: First clinical decompensation in patients with varices, mortality

In patients with **decompensated** disease:

- HVPG 16 mmHg: Variceal rebleeding, mortality
- HVPG 20 mmHg (in patients with active variceal hemorrhage): Failure to control active variceal hemorrhage, low one-year survival
- HVPG 22 mmHg: Mortality in patient with alcoholic cirrhosis and acute alcoholic hepatitis
- HVPG 30 mmHg: Spontaneous bacterial peritonitis



Hemodynamics in NCPF/IPH. Both intrasplenic (ISP) and intravariceal pressures (IVP) are high in NCPF. There are two independent pressure gradients – one between ISP and intrahepatic pressure (IHP) (8.9mmHg), and another between IHP and wedge hepatic venous pressure (WHVP) (6.2mmHg), indicating **2 patho-anatomic sites of resistance** in these cases – *presinusoidal* and *perisinusoidal*. As the vascular resistance is pre- and peri-sinusoidal, HVPG remains nearly normal

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Pre-hepatic		
FHVP normal, RAP normal, WHVP normal, HVPG normal, PVP high, ISP high		
Extrahepatic portal vein obstruction (EHPVO)		
Portal vein thrombosis		
Splenic vein thrombosis		
Splanchnic arteriovenous fistula		
Massive splenomegaly		
Infiltrative diseases-Lymphoma, myeloproliferative disorders		
Storage diseases-Gaucher's disease		
Hepatic		
FHVP normal, RAP normal, WHVP high, HVPG normal or high, PVP high, ISP high*		
Pre-sinusoidal	**Sinusoidal**	**Post-sinusoidal**
Developmental abnormalities	Sinusoidal fibrosis	Venoocclusive disease
Adult polycystic disease	Alcoholic hepatitis	Hepatic irradiation
Hereditary hemorrhagic disease	Drugs (methotrexate, amiodarone)	Toxins-Pyrrolizidine alkaloids
Arteriovenous fistulas	Toxins (vinyl chloride, copper)	Drugs-Gemtuzumab, ozogamicin, actinomycin D, dacarbazine, cytosine arabinoside, mithramycin, 6-thioguanine, azathioprine, busulfan plus cyclophosphamide
Congenital hepatic fibrosis	Metabolic (NASH, Gaucher's disease)	
Biliary diseases	Inflammatory (viral hepatitis, Q fever, healed cytomegalovirus, secondary syphilis)	
Primary biliary cirrhosis		
Sclerosing cholangitis		
Autoimmune cholangiopathy	Sinusoidal collapse	Phlebosclerosis of hepatic veins
Toxic-Vinyl chloride	Acute necro-inflammatory diseases	Alcoholic liver disease
Neoplastic occlusion of portal vein	Sinusoidal defenestration	Chronic radiation injury
Lymphoma	Alcoholic liver disease (early phase)	Hypervitaminosis A
Epithelioid hemangioendothelioma	Sinusoidal infiltration	E-ferol injury
Epithelial malignancies	Mastocytosis	Primary vascular malignancies
Chronic lymphocytic leukemia	Agnogenic myeloid metaplasia	Epithelioid hemangioendothelioma
Granulomatous lesions	Gaucher's disease	Angiosarcoma
Schistosomiasis	Amyloidosis	Granulomatous phlebitis
Mineral oil granuloma	Sinusoidal compression	Sarcoidosis
Sarcoidosis	By enlarged Kupffer cells (Gaucher's disease, visceral Leishmaniasis) By enlarged fat-laden hepatocytes (Alcoholic hepatitis, AFLP)	Mycobacterium species
Hepatoportal sclerosis		Lipogranulomas
Peliosis hepatitis		Mineral oil granuloma
Partial nodular transformation		Hepatic vein outflow tract obstruction (HVOTO, Budd-Chiari syndrome)-Idiopathic, prothrombotic states
Noncirrhotic portal fibrosis (NCPF)/ Idiopathic portal hypertension (IPH)		
Post-hepatic		
FHVP high, RAP normal or high, WHVP high, HVPG normal or high, PVP high, ISP high**		
Inferior vena cava obstruction-web, thrombosis, tumour, enlarged caudate lobe		
Constrictive pericarditis		
Tricuspid regurgitation		
Severe right-sided heart failure		
Restrictive cardiomyopathy		

Classification of noncirrhotic portal hypertension

Prehepatic
Portal vein thrombosis
Splenic vein thrombosis
Splanchnic arteriovenous fistula
Splenomegaly (eg, from lymphoma, Gaucher's disease*)
Intrahepatic
Presinusoidal
Schistosomiasis*
Idiopathic noncirrhotic portal hypertension (including nodular regenerative hyperplasia)
Primary biliary cholangitis
Sarcoidosis*
Congenital hepatic fibrosis
Primary sclerosing cholangitis
Hepatic arteriopetal fistula
Adult polycystic liver disease
Arteriovenous fistulas
Autoimmune cholangiopathy
Vinyl chloride toxicity*
Neoplastic occlusion of the intrahepatic portal vein
Mineral oil granuloma*
Sinusoidal
Arsenic poisoning
Vinyl chloride toxicity*
Drugs (eg, amiodarone, methotrexate)
Alcoholic liver disease*
Nonalcoholic fatty liver disease
Gaucher's disease*
Zellweger syndrome
Viral hepatitis
Chronic Q fever
Schistosomiasis*
Amyloid or light-chain deposition in the space of Disse
Acute hepatic injury
Mastocytosis
Agnogenic myeloid metaplasia
Acute fatty liver of pregnancy
Postsinusoidal
Sinusoidal obstruction syndrome (venoocclusive disease)
Budd-Chiari syndrome*
Alcoholic liver disease*
Chronic radiation injury
Vitamin A toxicity
Epithelioid hemangioendothelioma
Angiosarcoma
Sarcoidosis*
Mycobacterium avium or *M. intracellulare* infection
Mineral oil granuloma*
Posthepatic
IVC obstruction (eg, Budd-Chiari syndrome*)
Cardiac disease (constrictive pericarditis, restrictive cardiomyopathy)

IVC: inferior vena cava.
* May cause noncirrhotic portal hypertension via several mechanisms.

Schouten JN, Garcia-Pagan JC, Valla DC, Janssen HL. Idiopathic noncirrhotic portal hypertension. Hepatology 2011; 54:1071.

NCPH

- **Extrahepatic causes**

Disorders affecting the pre-hepatic or post-hepatic vascular system may result in non-cirrhotic portal hypertension.

- Pre-hepatic causes:

  portal or splenic vein thrombosis

  splanchnic arteriovenous fistulas

splenomegaly (eg, due to lymphoma or Gaucher disease).

- Post-hepatic causes

  obstruction of the hepatic veins or the inferior vena cava (eg, from Budd-Chiari syndrome)

cardiac diseases (eg, constrictive pericarditis and restrictive cardiomyopathy).

Intrahepatic causes:

may be presinusoidal, sinusoidal, or postsinusoidal.

- **Presinusoidal causes**
- Developmental abnormalities (eg, adult polycystic liver disease, congenital hepatic fibrosis, arteriovenous fistulas)
- Biliary diseases (eg, biliary cirrhosis, autoimmune cholangiopathy, primary sclerosing cholangitis, toxic biliary injury from vinyl chloride)
- Neoplastic occlusion of the intrahepatic portal vein (eg, due to lymphoma, epithelioid hemangioendothelioma, epithelial malignancies, chronic lymphocytic leukemia)
- Granulomatous liver lesions (eg, schistosomiasis, mineral oil granuloma, sarcoidosis)
- Idiopathic noncirrhotic portal hypertension

- **Sinusoidal causes**
- Fibrosis of the space of Disse, which may be metabolic (eg, nonalcoholic fatty liver disease, Zellweger syndrome), inflammatory (viral hepatitis, chronic Q fever, prior cytomegalovirus, schistosomiasis), or induced by drugs or toxins (eg, amiodarone, methotrexate, alcohol, vinyl chloride, copper)
- Amyloid or light-chain deposition in the space of Disse
- Defenestration of the sinusoidal lining in early alcoholic liver disease
- Sinusoidal destruction or collapse in the setting of acute hepatic injury
- Infiltrative diseases such as mastocytosis, Gaucher disease, and agnogenic myeloid metaplasia
- Compression of sinusoids by markedly hypertrophied hepatocytes, which may be seen with microvesicular steatosis

- **Postsinusoidal causes**
- Sinusoidal obstruction syndrome (venoocclusive disease)
- Budd-Chiari syndrome
- Phlebosclerosis of hepatic veins (eg, due to alcoholic liver disease, chronic radiation injury, hypervitaminosis A)
- Primary vascular malignancies (eg, epithelioid hemangioendothelioma, angiosarcoma)
- Granulomatous phlebitis (eg, from sarcoidosis, *Mycobacterium avium* or *M. intracellulare* infection)
- Lipogranulomas (eg, mineral oil granuloma)

IDIOPATHIC NONCIRRHOTIC PORTAL HYPERTENSION

- Nodular regenerative hyperplasia
- Noncirrhotic portal fibrosis
- Idiopathic portal hypertension
- Hepatoportal sclerosis
- Incomplete septal cirrhosis
- Obliterative portal venopathy
- Benign intrahepatic portal hypertension
- Idiopathic presinusoidal portal hypertension
- Partial nodular transformation

- 14 to 27 % of NCPH
- Etiology: unknown

Several pathophysiologic mechanisms believed to be involved

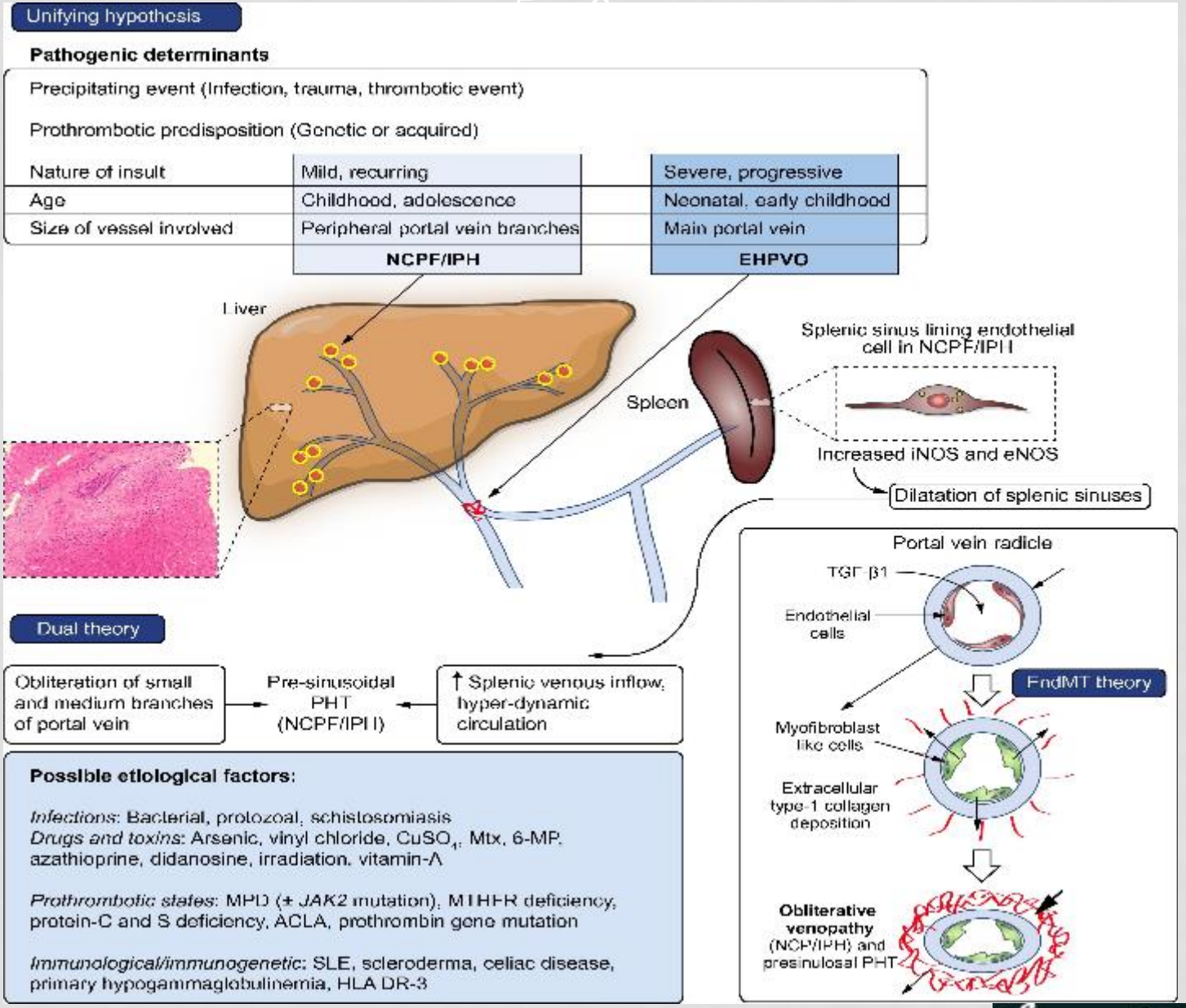
- Chronic or recurrent infections – Repeated episodes of umbilical sepsis, bacterial infections, and diarrhea in early childhood → portal pyemia and pylephlebitis →vascular endothelial injury, microthrombosis, sclerosis, and obstruction of small- and medium-sized portal vein radicals.
- Drugs & toxins: induce fibrosis
- HIV: HAART effect on microvasculature of the liver or the direct effect of the HIV itself
- Altered immune response
- Hypercoagulability
- Genetic: HLA-DR3
- Miscellaneous: role for endothelin-1, nitric oxide, and connective tissue growth factor

Disorders and medications associated with idiopathic noncirrhotic portal hypertension

Hematologic/neoplastic
Liver cancers
Sacrococcygeal teratoma
Essential thrombocytosis
Polycythemia vera
Myeloproliferative disorders
Lymphoproliferative disorders
Multiple myeloma
Spherocytosis
Sickle cell disease
Protein S deficiency
Factor V Leiden mutation
Hyperhomocysteinemia
Antiphospholipid syndrome
Immune
Primary biliary cholangitis
Polymyositis
Sjögren's syndrome
Scleroderma
CREST syndrome
Still's syndrome
Polyarteritis nodosa
Rheumatoid arthritis
Polymyalgia rheumatica
Systemic lupus erythematosus
Behçet's syndrome
Cryoglobulinemia
Idiopathic hypereosinophilic syndrome
Idiopathic thrombocytopenic purpura
Celiac disease
Myasthenia gravis
HIV infection
Common variable immunodeficiency

Medications
Azathioprine
Thioguanine
Cyclophosphamide
Chlorambucil
Busulfan
Doxorubicin
Cytosine
Arabinoside
Bleomycin
Carmustine
Trastuzumab
Interleukin-2
Miscellaneous
Liver transplantation
Renal transplantation
Atrial septal defect
Ventricular septal defect
Pulmonary vein anomalies
Congenital portal venous anomalies
VATER syndrome
Hereditary hemorrhagic telangiectasia
Cystinosis
Turner's syndrome

HIV: human immunodeficiency virus; CREST: calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia; VATER: Vertebral anomalies, anal atresia, TE fistula (tracheoesophageal fistula), renal defects.



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- Typically, liver function is preserved, even when portal hypertension is clinically evident. Liver failure with ascites and/or encephalopathy is rare
- Most common clinical presentation is variceal bleeding
- Massive splenomegaly
- Liver biochemical tests are usually normal or nearly normal
- Anemia, leukopenia, and thrombocytopenia are common because of hypersplenism

Diagnosis of idiopathic noncirrhotic portal hypertension requires that all of the following criteria be met:

- **Clinical signs of portal hypertension** (at least one of the following):
- Splenomegaly/hypersplenism in conjunction with another sign of portal hypertension
- Esophageal and/or gastric varices
- Ascites (nonmalignant)
- Increased hepatic venous pressure gradient
- Portovenous collaterals

- **Exclusion of cirrhosis on liver biopsy**
- **Exclusion of chronic liver disease**
- **Exclusion of other causes of non-cirrhotic portal HTN**
- **Imaging showing patent portal and hepatic veins**

HISTOLOGY

- idiopathic noncirrhotic portal hypertension classified into one of four histologic categories:

- Idiopathic portal hypertension was defined by the presence of fibrotic portal tracts and thin fibrous septa without evidence of cirrhosis.
- Nodular regenerative hyperplasia was defined by micronodular transformation of the liver parenchyma, with central hyperplasia, an atrophic rim, and no fibrosis.
- Partial nodular transformation was characterized by noncirrhotic, grossly visible parenchymal nodules that are located in the perihilar region of the liver around the large portal tracts.
- Incomplete septal cirrhosis was defined by slender, incomplete septal fibrosis that demarcates the liver parenchyma into nodules. The portal tracts are hypoplastic and hepatocytes are hyperplastic.

common finding associated with idiopathic noncirrhotic portal hypertension is obliteration of small portal venules (occlusive venopathy)

HEMODYNAMICS

- Despite unequivocal signs of portal hypertension such as large esophageal varices and splenomegaly, HVPG values in patients with idiopathic noncirrhotic portal hypertension are much lower than the cutoff for clinically significant portal hypertension in cirrhosis

IMAGING

- Ultrasonography: Isoechoic nodules.
- CT scan: Nonspecifically hypodense nodules
- MRI: Isointense nodules on T2-weighted images that contain foci of high intensity on T1-weighted images
- Fibroscan: liver stiffness value on transient elastography is far below what would be expected in a patient with cirrhosis.

- Management and prevention of variceal hemorrhage: early pharmacologic treatment with vasoactive drugs, early endoscopic control of bleeding, careful blood product replacement, and prophylactic antibiotics
- TIPS or splenectomy
- Primary and secondary prevention of variceal bleeding includes the use of nonselective beta blockers and endoscopic variceal ligation.

- Prognosis: better than that of patients with cirrhosis who have a similar degree of portal hypertension

Currently, screening for hepatocellular carcinoma is not recommended

SCHISTOSOMIASIS

- Most common causes of noncirrhotic portal hypertension worldwide
- *S. japonicum* and *S. mansoni*
- Chronic hepatic schistosomiasis is characterized by features of portal hypertension: esophageal varices, hepatomegaly, and splenomegaly with hypersplenism.
- Diagnosis: detection of schistosomal ova in the stool.
- Management: treating underlying parasitic infection (Praziquentel) and preventing or treating the consequences of portal hypertension.

- Enter the body through the skin→ adult worms eventually inhabit tributaries of the inferior (*S. mansoni*) or superior (*S. japonicum*) mesenteric veins, where they produce 100-1000s eggs per day for several years→ become trapped in the terminal portal venules, where they induce chronic inflammation →marked fibrosis.

- Hyperdynamic systemic and splanchnic circulation with normal hepatic venous pressure gradient

PORTAL VEIN THROMBOSIS

- Patients with acute PVT have the sudden onset of portal venous occlusion due to thrombus.
- may be complete or partial.
- clot may also involve the mesenteric veins or the splenic vein.
- Silent, abdominal pain, fever, variceal bleeding
- primary management of acute portal vein thrombosis (PVT) is anticoagulation and, when possible, treatment of predisposing conditions for at least three to six months

BUDD-CHIARI SYNDROME

- Hepatic venous outflow tract obstruction
- fever, abdominal pain, abdominal distension (from ascites), lower extremity edema, jaundice, gastrointestinal bleeding (from varices or portal hypertensive gastropathy), and/or hepatic encephalopathy
- US doppler, CT or MRI
- Treatment: anticoagulation, thrombolytics, angioplasty +/- stenting, TIPS

Major causes of the Budd-Chiari syndrome

Myeloproliferative diseases
Malignancy
Hepatocellular carcinoma is most common
Infections and benign lesions of the liver
Hypercoagulable states
Oral contraceptive use
Pregnancy
Factor V Leiden mutation
Prothrombin gene mutation
Antiphospholipid antibody syndrome
Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Paroxysmal nocturnal hemoglobinuria
JAK2 mutations
Behçet's disease
Membranous webs of the inferior vena cava and/or the hepatic veins
Miscellaneous conditions including celiac disease, ulcerative colitis, hypereosinophilic syndrome, and granulomatous venulitis
Idiopathic
Many may have an underlying myeloproliferative disease

SINUSOIDAL OBSTRUCTION SYNDROME/VENO-OCCLUSIVE DISEASE

occlusion of the terminal hepatic venules and hepatic sinusoids → venous endothelial injury

- hematopoietic cell transplantation
- following the use of chemotherapeutic agents in non-transplant settings
- ingestion of alkaloid toxins or herbals
- after high dose radiation therapy (> 30 Gy)
- liver transplantation

The modified Seattle criteria define hepatic SOS by the otherwise unexplained occurrence of two or more of the following events within 20 days of HCT:

- Serum total bilirubin concentration > 2 mg/dL(Jaundice)
- Hepatomegaly or right upper quadrant pain
- Sudden weight gain due to fluid accumulation (>2 % of baseline body weight)

The Baltimore criteria define hepatic SOS by a bilirubin >2 mg/dL (jaundice) within 21 days of HCT plus at least two of the following:

- Hepatomegaly
- Ascites
- Weight gain >5 percent from pre-HCT weight

CONGENITAL HEPATIC FIBROSIS

- rare developmental disorder, mostly autosomal recessive
- ductal plate malformation (DPM), producing irregularly shaped proliferating intrahepatic bile ducts and periportal fibrosis ultimately leading to PHT
- Associations: ARPKD, Caroli disease, Choledochal cyst or isolated
- Esophageal varices and hypersplenism are present in 40–78% and 44–75%, respectively, cholangitis
- Increased predisposition to cholangiocarcinoma
- CLKT is the best available option

MTX

- Patients on long term MTX (after 2-10 yrs, cumulative dose of 4 gms) present with signs and symptoms of portal hypertension, yet have only moderate degrees of fibrosis, suggesting that methotrexate may also cause nodular regeneration.

- Direct toxicity: increase hepatic stellate cell numbers, but the mechanism by which fibrosis is induced has not been clearly elucidated.

FIBROSCAN

- TE is useful in differentiating cirrhosis from non-cirrhotic portal hypertension.

Pts with non-cirrhotic portal HTN (biopsy proven), extra-hepatic portal HTN (portal vein cavernoma +/- splenic vein cavernoma w/out liver disease), compared to healthy controls.

- Variceal bleed at presentation was more common in males & older age pts with non-cirrhotic portal HTN.

- Liver stiffness was higher in patients with non-cirrhotic portal HTN & extra-hepatic portal HTN as compared to normal individuals. Stiffness value of < 10.5 kPa had sensitivity and specificity of 78.1 % & 82.3 % to differentiate it from cirrhosis with AUROC of 0.89.

Parikh HR et al. Seth GS Medical college & KEM hospital, Mumbai, India

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THANK YOU