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2nd Edition

Ashis Kumar Saha

Foreword
Gurpreet S Wander

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Section 1 Hepatology

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PGI/NOV2012 (10)

Discuss biochemical defect and management of a child with Wilson's disease.

BF/JUNE2016/MDI (10)

Wilson's disease.

MGR/MAR2006/MDIV (5)

MGR/MAR2008/MDIV (6)

Diagnosis and management of Wilson's disease.

DNB (DEC2022) (10)

Diagnosis of Wilson's disease

DNB (DEC2020) (4)

Bilirubin synthesis and metabolism. Diagnosis and treatment of Wilson's disease.

DNB (DEC2019) (10)

Wilson disease clinical manifestations and diagnosis.

DELHI UNI, 2024 (10)

Management of Wilson's disease.

KERALA UNIVERSITY, 2019 (10)

Write the diagnosis and management of Wilson's disease.

MANIPUR UNIVERSITY, 2019 (10)

ANSWER

Wilson's disease is a rare inherited familial disorder characterized by progressive neurological features with evidence of cirrhosis and Kayser–Fleischer (K–F) ring in the cornea.

Pathogenesis

There are two genes responsible for metal-transporting enzyme P-type ATPase (adenosine triphosphatase):

A. One is ATP7A; it is abnormal in Menkes disease.

B. The other is ATP7B found in chromosome 13; ATP7B is present in liver, kidney, and in small amount in brain, placenta, and lung. This gene product is Wilson-ATPase in intracellular.

Transport of copper and its defect in homeostasis:

Copper is present in plasma in cupric form bounded with albumin and histidine. Cupric form must be transformed to cuprous form prior to intake by hepatocytes. It is transported into hepatocytes in cuprous form via the copper-binding N-terminal domain of transmembrane transporter (CTR1). But in presence of high concentration of copper CTR1 will be degraded leading high rise of nonceruloplasmin-bounded copper—it is responsible for neurological manifestation of Wilson's disease prior to hepatocellular necrosis.

Now within the hepatocytes coppers bound to low-molecular protein metallochaperones, it will ultimately directs the copper molecules to the following molecules:

A. Some coppers metallothioneins store copper as non-toxic form.

B. Some coppers form complexes with glutathione.

C. Intracellular ceruloplasmin such as ferroxidase oxidizes iron from iron to transferrin. When ceruloplasmin is devoid of copper it is called apoceruloplasmin. When intracellular copper combines with apoceruloplasmin, holoceruloplasmin is formed, it is enzymatically active.

D. CCS1 protein delivers the copper to Cu/Zn superoxide dismutase.

E. COX17 delivers copper to subunit II cytochrome c oxidase within the mitochondria mediated by SCO1 and SCO2.

F. ATOX1 by virtue of its copper-binding domain CXXC will transport copper Wilson ATPase present in the trans-Golgi network region. Now Wilson-ATPase has two-fold of actions:

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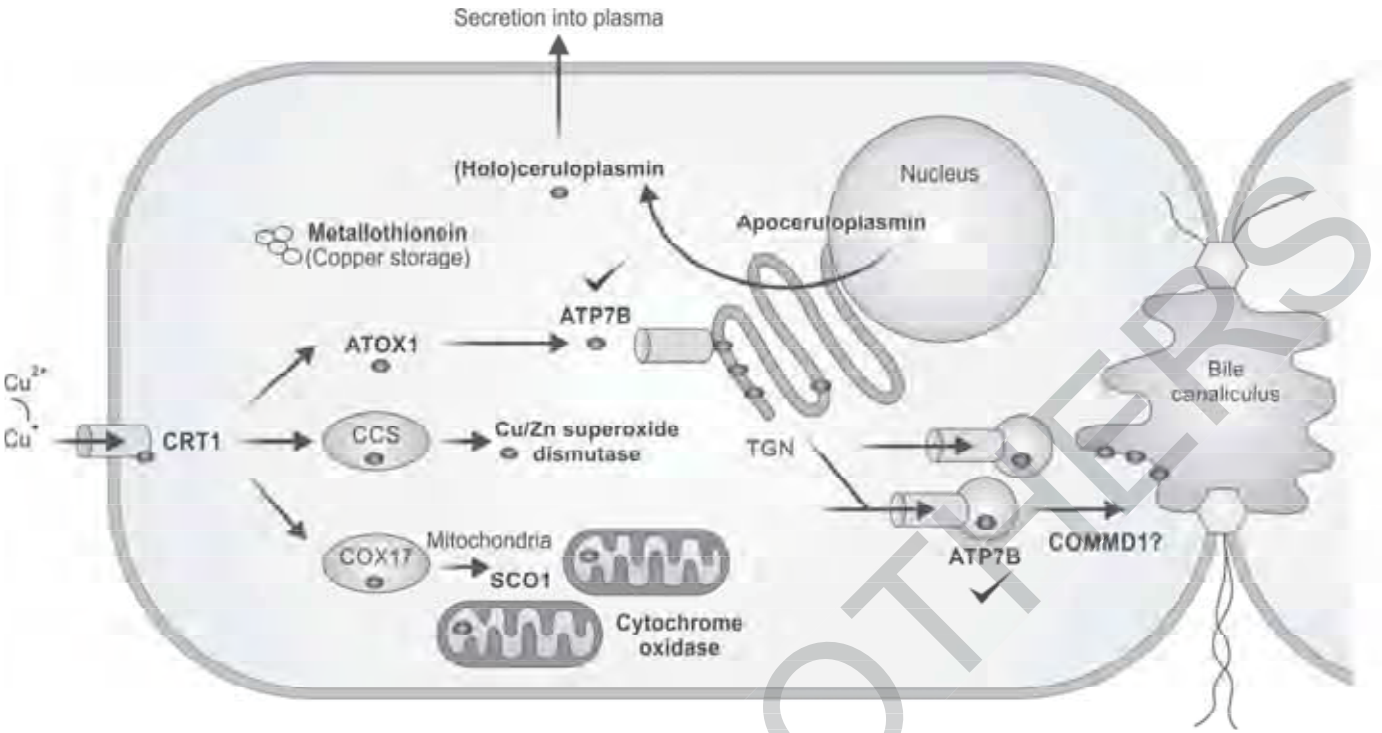

a. It will incorporate copper into apoceruloplasmin.

b. It will help in excretion of copper into biliary canaliculi.

If the intracellular concentration of copper will be elevated Wilson ATPase redistributes to the apical region of hepatocytes near the area of biliary canalicular membrane.

When the concentration of copper is elevated Wilson ATPase moves to lysozyme and imports copper into the lumen where it interacts with p62 subunit dynactin and translocate lysozyme toward canalicular pole and release copper into the bile. This exocytosis is governed by a gene *COMMDI*. Protein encoded by *COMMDI* will interact with copper-binding domain of Wilson's ATPase, ATP7B. It inhibits transcription factor κβ and thus affects immune response as well as cell cycle regulation.

So defect in ATP7B for the copper-related damage of hepatocytes is in the following ways:

Being prooxidant accumulated copper produces liver damage by oxidative stress through "Fenton-type" reaction. Generated peroxides and hydroxyl radicals in this reaction produce damage of deoxyribonucleic acid (DNA) in hepatocytes.

In the brain action of copper is regulated by amyloid protein. If the concentration of copper in brain will be increased or the activities of key copper-containing enzymes are altered, both will lead to neuronal damage in brain.

Other mechanisms in case of Wilson's disease are:

A. Focal deletion of DNA in mitochondria found usually in aging.

B. Antioxidant vitamin E is found in untreated Wilson's disease.

C. There is evidence of increased mutation of tumor suppressor gene *TP53*.

D. Nitric oxide synthase (NOS) will be increased.

So natural history of Wilson's disease is divided into four stages:

A. Stage 1: In this initial period accumulation of copper present within hepatic binding sites.

B. Stage 2: Acute redistribution of copper in the liver and its release into the circulation.

C. Stage 3: In this stage, there is chronic accumulation of copper within the brain along with other extrahepatic tissues and eventually fatal disease.

D. Stage 4: Long-term chelation therapy will restore the copper balance.

Clinical Features in Wilson's Disease

A. Different spectrum of liver diseases:

- **a.** Acute hepatitis
- **b.** Chronic hepatitis
- **c.** Decompensated or compensated cirrhosis
- **d.** Acute fulminant hepatic failure
- **e.** Persistent transaminases elevation

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B. Neurological manifestation:
- **a.** Extrapyramidal manifestations, such as cognitive decline, tremor, dysarthria, seizures, and abnormal gait
- **b.** Myoclonus
- **c.** Chorea
- **d.** Insomnia
- **e.** Metabolic myopathy

C. Psychiatric manifestations:
- **a.** Depression
- **b.** Personality changes
- **c.** Bipolar disorders
- **d.** Schizophrenia
- **e.** Mental retardation

D. Eye changes:
- **a.** Sunflower cataract
- **b.** K–F ring

E. Hematological manifestations:
- **a.** Anemia
- **b.** Bleeding gum
- **c.** Hematemesis

F. Genitourinary abnormalities:
- **a.** Menstrual irregularities
- **b.** Acute tubular necrosis

Most important complication is Wilsonian fulminant hepatic failure. It occurs mainly in 10–30 years females. This complication can be differentiated from liver failure of other etiologies by combining the clinical and biochemical features together.

Biochemical features are:

A. Disproportionate low level of aminotransferases to <2,000 U/L from the onset of this disease.

B. Serum alkaline phosphatase (ALP) level is normal or mildly reduced.

C. Bilirubin level is highly increased where there is associated hemolysis.

D. Following biochemical index is suggestive of this failure (calculated in American unit):
- **a.** Ratio of ALP to serum bilirubin is <4
- **b.** Ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT) is <2.2
- **c.** In case of children ratio of ALP to bilirubin level is <1
- **d.** NAZZER index: It is based on serum AST, bilirubin concentration, and prolongation of prothrombin time (PT); it identifies Wilsonian failure but cannot detect the prognosis of the failure.

E. Associated intercurrent viral illness or hepatitis C may precipitate liver failure in case of Wilson's disease.

Management

Drugs recommended for treating the Wilson's disease:

Disease state	First choice	Second choice
Hepatitis or compensated cirrhosis	Zinc	Trientine
Decompensated cirrhosis		
Mild	Trientine and zinc	Penicillamine and zinc
Moderate	Trientine and zinc	Liver transplantation
Severe	Liver transplantation	Trientine and zinc
Initial neurologic or psychiatric features	Tetrathiomolybdate and zinc	Zinc
Maintenance	Zinc	Trientine
Presymptomatic	Zinc	Trientine
Pediatric	Zinc	Trientine
Pregnant	Zinc	Trientine

Drugs with dosages and side-effects:

Drugs	Dose	Efficacy assessment	Monitoring of side effects
D-penicillamine	• Initially 1–1.5 g/day in twice or thrice equally divided doses • Maintenance dose is 0.75–1 g/day in thrice equally divided doses	Target is 24 h urinary copper excretion 200–500 µg/day	• Complete blood count • Dermatological examination • Urinalysis
Trientine	• Initially 1–1.5 g/day in twice or thrice equally divided doses • Maintenance dose is 1–1.5 g/day in thrice equally divided doses	Target is 24 h urinary copper excretion 200–500 µg/day	• Complete blood count • Serum iron and iron-binding capacity • Urinalysis
Zinc	• Initially 50 mg elemental zinc orally thrice daily ≥1 h meals • Maintenance dose is titration of the dose as required to achieve the efficacy	Target is 24 h urinary copper excretion <0.75 µg/day	• Serum creatinine, zinc (to monitor adherence) • Urinalysis • Serum AST and ALT

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In case of decompensation of liver following score as suggested by Nazer has to be followed:

Laboratory test	Normal value	Score				
		0	1	2	3	4
Bilirubin	0.2–1.2 mg/dL	<5.8	5.8–8.8	8.8–11.7	11.7–17.5	>17.5
AST	10–35 IU/L	<100	100–150	151–200	201–300	>300
Prolongation of prothrombin time	→	<4	4–8	9–12	13–20	>20

Note: If the score is <7—oral therapy will be recommended.

If the score is >9—liver transplantation is recommended.

If the score is between 7 and 9, then clinical judgment is required whether oral therapy or transplantation is best for that patient.

If the score is >9 bridge should be combination of zinc and trientine prior to transplantation.

Q2. Discuss etiology, clinical features, investigations and management of acute liver failure.

MUHS/NOV2010/MDIII (25)

Describe pathophysiology, clinical features, complications, and management of acute hepatic failure.

MUHS/MAY2010/MDIII (25)

Management of acute hepatic failure.

BF/MAY2010/MDIII (10)

Discuss etiology, clinical features and management of acute liver failure.

ERA/MAY2012/MDII (15)

Discuss etiology, clinical features, prognostic markers and management of acute liver failure.

DNB/JUNE2012 (10)

Clinical manifestations of liver dysfunction.

SCB MED COL, 2017 (20)

Define fulminant hepatic failure. Describe its clinical features, investigations and management.

MAHARASHTRA UNI OF HEALTH SC. 2022 (25)

Acute liver failure.

TEERTHANKER MAHAVEER UNIVERSITY, 2018 (10)

ANSWER

Definition

Acute liver failure is a devastating syndrome characterized by impairment of liver function test, such as hemodynamic instability, coagulopathy, cerebral edema, renal failure, severe metabolic disturbances, and propensity to develop bacterial or fungal infections.

Acute liver failure is divided into three subtype depending upon the appearance of jaundice and development of hepatic encephalopathy:

A. Hyperacute or fulminant liver failure, the interval is <2 weeks.

B. Acute or subfulminant liver failure where the interval is >2 weeks but <8 weeks.

C. Subacute liver failure where the interval is >8 weeks but <24 weeks.

Etiology

A. Infections:
- **a.** Hepatitis A, B, C, D, and E
- **b.** Epstein–Barr virus
- **c.** Dengue fever
- **d.** Herpes simplex virus

B. Drugs and toxins:
- **a.** Acetaminophen
- **b.** Carbon tetrachloride
- **c.** Idiosyncratic drug reactions
- **d.** Mushroom poisoning

C. Ischemic:
- **a.** Hypotension
- **b.** Heat stroke
- **c.** Cardiogenic stroke

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D. Vascular causes:
  a. Acute Budd–Chiari syndrome
  b. Sinusoidal obstruction syndrome
E. Acute liver failure of pregnancy
F. Wilson's disease
G. Malignancy

Spectrum of liver damage histologically according to etiologies of hepatic failure:
A. Confluent necrosis (+ activation of nonparenchymal cells, Kupffer cells, stellate cells, endothelial cells)—drugs such as acetaminophen, toxins, viruses, and ischemia
B. Microvascular steatosis—drugs such as tetracycline, valproic acid, mitochondrial toxins, and fatty liver of pregnancy
C. Malignant infiltration—metastatic deposits, leukemia, and lymphoma

Molecular mechanism of cell injury and death:
Death of hepatocytes is of two types:
A. Apoptosis: Here there is shrinkage of cytoplasm and cell nucleus without disruption of the cell membrane integrity and release of liberation of intracellular content. So, there is no secondary inflammation. It occurs following sequential activation of cysteine proteases called Caspases. There are two mechanisms by which apoptosis can occur:
  a. Extrinsic mechanism: Here death receptor is present on the cell membrane
  b. Intrinsic mechanism: Here oxidative stress of mitochondria and endoplasmic reticulum are responsible.

  Caspase-8 and 9 mediate signals for extrinsic and intrinsic mechanisms, respectively.
B. Necrosis: Here as a consequence of depletion of adenosine triphosphate cell will swell followed by disruption of membrane and release of cell content associated with secondary inflammation.

Pathophysiology

A. Hemodynamic changes:
  a. Marked splanchnic vasodilatation
  b. Marked systemic arteriolar vasodilatation
  c. Hyperdynamic vasodilatation
  d. Low arteriovenous oxygen difference. It may be due to endothelial damage, generation of oxygen-free radicals, production of vasoactive cytokines and microcirculatory plugging by platelet-rich thrombi, and increased adhesion to endothelium by leukocytes.
B. Hepatic encephalopathy: It occurs due to cerebral edema as a result of following mechanisms:
  a. Accumulation of ammonia
  b. Disturbances in different pathways, such as glutamatergic, noradrenergic, and serotonergic pathways
  c. Accumulation of false neurotransmitters
  d. Activation of γ-aminobutyric acid receptors
  e. Altered metabolism of cerebral energy
  f. Failure of autoregulation with cerebral perfusion due to cerebral vasodilatation and impaired cerebral resistance vessel constriction in response to systemic arterial pressure
C. Renal impairment: It may occur through following mechanisms:
  a. Relative hypovolemia due to:
    1. Vasodilatation
    2. Microcirculatory disturbances
    3. Vasodilatation
    4. Acute tubular necrosis due to sepsis
    5. Direct nephrotoxic injury by acetaminophen
D. Susceptibility to infection: Patients are susceptible to infection due to following mechanisms:
  a. Impaired phagocytic function of neutrophils
  b. Impaired phagocytic function of Kupffer cells
  c. Reduced complement function by hepatocytes
  d. Different types of invasive procedures
  e. Increased translocation of bacteria from the gut

  Infective organisms are bacteria and fungi. Sometime these patients may be afebrile with normal white blood cell count.
E. Nutritional disturbances:
  a. Energy requirement in these patients is nearly increased up to 60% with mean energy expenditure is 4.05 kJ/kg/h in spite of reduction of liver cell mass.
  b. Glycogen storage capacity and gluconeogenesis will be reduced
  c. Increased breakdown of skeletal muscles
  d. Impaired whole body protein degradation due to:
    1. Reduced synthesis of insulin-like growth factor-1
  e. Electrolyte disturbances, such as hyponatremia, hypokalemia, hypophosphatemia, and hypomagnesemia
  f. Hypoglycemia
F. Coagulation disorders may develop due to following:
  a. Reduced synthesis of clotting factors leading to impaired coagulation and anticlotting factors,

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like protein S and C and antithrombin III leading to microvascular thrombosis and thus producing clogging of dialysis circuit.

b. Consumption of clotting factors and platelets due to disseminated intravascular coagulation.

G. Platelet abnormality due to following:

a. Thrombocytopenia

b. Increased adhesion and impaired aggregation of platelets

Clinical Manifestations

A. Symptoms such as malaise, nausea, vomiting, progressively increasing yellow discoloration of eyes and dark urine, fever, progressively increasing alteration in consciousness, bleeding abnormalities, gastrointestinal bleeding, and wasting

B. Signs include:

a. General signs such as anemia, jaundice, tachycardia, hypotension, and tachypnea in case of respiratory infections

b. Loss of hepatic mass leading to shrunken liver which can be palpable in midclavicular line

c. Features of hypoglycemia

d. Features of electrolyte disturbances

C. In case of subacute and chronic liver failure ascites, edema, cerebral edema, renal failure, features of chronic liver disease, and hypotension.

Investigations

A. Hematology:

a. Complete blood count to detect anemia due to disease and bleeding

b. WBC—it is increased in case of infection.

c. Hematocrit

d. Hemoglobin

e. Blood group

B. Biochemical tests:

a. Liver function test: Bilirubin level >10 mg/dL and aminotransferase level >3,500 IU/L are suggestive of paracetamol toxicity.

b. Serum electrolytes

c. Urea and creatinine

d. Fasting serum glucose

e. Serum ceruloplasmin, copper, and cortisol level at 8 AM

f. Cosyntropin test to detect Addison's disease

C. Virology:

a. Viral profile of hepatitis B, C, D. D virus should be sought if the patient is hepatitis B virus (HBV) positive.

b. If the patient is HBV or HCV positive, HBV DNA or HCV RNA (ribonucleic acid) has to be done.

c. In case of endemic areas immunoglobulin M (IgM) HAV and IgM HEV are indicated.

d. Polymerase chain reaction (PCR) for cytomegalovirus or herpes simplex virus and Epstein–Barr virus in immunosuppressed patients

e. HIV screening

D. Toxicology screening:

a. Drug

b. Toxin

c. Alcohol

d. Urine drug screening

E. Autoimmune disorders:

a. Antinuclear antibody (ANA)

b. Antismooth muscle cell antibody

c. Anti-liver-kidney microsomal (LKM) antibody

F. Microbiology:

a. Culture of aerobic and anaerobic blood culture

b. Urine microscopy and culture

c. Sputum microscopy and culture

G. Radiological investigations:

a. Ultrasound of abdomen to detect liver condition, spleen, pregnancy or not.

b. Electroencephalogram (EEG)—slowing of cortical activity in 50% patients with liver disease with epileptiform activity. There are five grades found in EEG in this disease.

1. Grade A to D—wave of decreasing frequency but increasing amplitude—it suggests increasing drowsiness.

2. At D—triphasic wave appears.

3. There is an interrupted line at D—on the right of that line recovery is unlikely.

4. From E to F grade—amplitude decreases but frequency changes little—it suggests patient is going to deep unconsciousness.

5. At F grade—there is no cerebral activity.

c. CT scan of brain—it can rule out cerebral hemorrhage in case of unconscious patients.

d. Chest X-ray to detect hepatic hydrothorax, or infective features

e. Doppler ultrasound of portal vein to see any obstruction, reversal of flow

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H. Invasive studies:
- **a.** Liver biopsy to detect status of liver architecture, vascular pattern, reduction in liver size, viral inclusions, and copper estimation
- **b.** Drainage of ascetic fluid to detect character of the fluid, culture

I. Miscellaneous studies:
- **a.** 24-hour urinary copper
- **b.** Pregnancy test

Treatment

Treatment of liver failure mainly consists of treatment of complications and treatment of the etiologies.

Treatment of Hepatic Encephalopathy

Neurological support is aimed at:

A. Optimizing cerebral blood flow

B. Optimizing cerebral perfusion pressure

C. Oxygen administration

D. Treatment of cerebral edema

So, management is:

A. Head end should be elevated by 30°

B. Elective mechanical ventilation with muscle paralysis with propofol, minimal endotracheal suctioning, and tactile stimulation to prevent surge of intracranial pressure (ICP)

C. Infusion of prostacyclin can be given

D. International normalized ratio (INR) and platelet count should be 2 or less and 50,000/cc, respectively prior to introduction of transducer which can guide the therapy in patient with grade III or IV encephalopathy. But it should be removed within 5 days as there is chance of infection and bleeding.

E. Cerebral perfusion pressure = Mean arterial pressure – Intracranial pressure
- **a.** If it is <50 mm Hg due to hypotension, it has to be corrected by vasopressor agents but intravascular volume is normal.
- **b.** If cerebral perfusion pressure is low due to increased ICP or if later is increased >25 mm Hg, intravenous 20% mannitol has to be administered at a rate of 0.25–1 g/kg and it can be repeated if the serum osmolarity is <320 mOsm/L
- **c.** If there is volume overload and the patient is oliguric renal replacement therapy should be given.

F. To induce cerebral vasoconstriction to reduce cerebral flow hyperventilation can be tried or in some cases intravenous indomethacin to treat refractory intracranial hypertension.

G. In case of impending herniation:
- **a.** Thiopentone has to be given in bolus dose of 5–10 mg/kg intravenously followed by 3–5 mg/kg/h; or
- **b.** Phenobarbital at a dose of 3–5 mg/kg bolus intravenously followed by 1–3 mg/kg slow infusion

H. Induction of hypothermia to core body temperature to 32–33°C with cooler blankets for period of 10–118 hours may reduce ICP by reduction of cerebral blood flow, glutathione synthesis, and decreasing the arterial ammonia.

I. Correction of acidosis and electrolytes:
- **a.** Administration of hypertonic saline to raise the serum sodium 145–155 mmol prophylactically in case of severe encephalopathy.

Lactulose: But it has been shown having no benefit because of following reasons:
- **a.** There is chance of aspiration
- **b.** Bowel distension which complicates transplantation.

Treatment of Coagulopathy

A. If platelet is <10,000/cc—platelet transfusion should be given.

B. In case of any active procedure required or there is active bleeding—fresh frozen plasma (FFP) has to be given.

C. If the coagulopathy is refractory to FFP then 40 µg/kg recombinant factor VII has to be given 30 minutes before the procedure.

D. In case of severe bleeding with fibrinogen level of <100 mg/dL cryoprecipitate should be administered.

E. If INR is >1.5, injection of vitamin K has to be given through intravenous or intramuscular route required.

F. In case of requirement of large amount of FFP, plasmapheresis is of choice.

G. Prophylactically for stress ulceration proton-pump inhibitor is required.

Treatment of Renal Failure

Renal complication in case of acute liver failure may occur due to the following:

A. Hepatorenal syndrome (HRS) due to lowering of renal perfusion pressure, sympathetic nervous system activation, decreased filtration through glomerulus, and increased vasoactive mediator synthesis

B. Direct nephrotoxicity to drugs

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Secondary complications due to bleeding, sepsis, and hypotension.

Treatment should be:

A. Administration of 1–1.5 L intravenous fluid to treat prerenal azotemia.

B. To increase renal perfusion pressure low-dose dopamine is to be given. Continuous renal replacement therapy with bicarbonate buffer is given in case of hemodynamically stable patients to prevent ICP fluctuation.

Treatment of Hemodynamic Changes

Hemodynamic changes are characterized by increased cardiac output in the face decreased peripheral vascular resistance.

Treatment:

A. Intravenous administration of crystalloid or albumin

B. Administration of vasopressors to maintain the mean arterial pressure of >60 mm Hg or cerebral perfusion of <50 mm Hg.

C. Administration of vasopressin to cause cerebral vasodilatation

D. If serum cortisol level is low intravenous hydrocortisone 200–30 mg/day may be beneficial.

Treatment of Infection

A. Prophylactic antibiotic treatment with surveillance for prompt antibiotic treatment

B. If the patient is not responding to antibiotic treatment, antifungal treatment should be given.

C. Invasive procedure should be done under strict aseptic control.

Treatment of Pulmonary Complication

A. To prevent increased intracranial hypertension sedation should be given in case of endotracheal intubation and suction.

B. If the patient is under ventilation following parameter should be followed:

- **a.** Tidal volume 6 mL/kg
- **b.** Low positive end-expiratory pressure
- **c.** $PaCO_2$ of 30–40 mm Hg

Treatment of Metabolic Causes

A. Treatment of electrolyte imbalance

B. In acute liver failure it is persistent and intractable. It produces neurological deterioration and death. If blood glucose is <60 mg/dL continuous infusion of 5–10% dextrose should be administered.

Treatment of Specific Causes

Paracetamol overdose:

A. N-acetyl cysteine can be given orally 140 mg/kg bolus followed by 70 mg/kg every 4 hourly for total 17 doses. It can be given intravenously at 150 mg/kg in 5% dextrose over 15 minutes followed by 50 mg/kg over 4 hours then 100 mg/kg over 16 hours.

Mushroom poisoning:

A. Gastric lavage with activated charcoal in case of acute ingestion with nausea and vomiting.

B. Most common antidote penicillin G at a dose of 300,000–1 million units/kg.

C. Silibinin at 30–40 mg/kg/day orally or intravenously along with or without N-acetyl cysteine is more effective.

Hepatitis B or C treatment: Effective antiviral treatment has to be given.

Herpes simplex treatment: It occurs mainly in immunosuppressed or pregnant patient. Diagnosis is suspected by vesicular rash with high aminotransferase level. Prognosis is poor in spite of acyclovir treatment.

Autoimmune hepatitis (AIH):

A. This patient has to be treated by prednisolone 60 mg/day.

B. If there is multilobar collapse, persistent elevated bilirubin, and the patient fails to respond to steroid within 2 weeks, transplantation is the treatment of choice.

Wilson's disease:

A. Penicillamine or trientine is the drug of choice.

B. Albumin dialysis

C. Plasmapheresis to remove copper

D. Continuous renal replacement therapy

Liver transplantation: It should be done in patient with grade III to IV hepatic encephalopathy due to hepatic failure. It is used on following validated criteria, such as age, pH, interval between onset of jaundice and encephalopathy, etiology, PT, raised bilirubin level, and <20% of normal factor V.

Contraindications

A. Malignancy

B. Infection

C. Brain death

D. Cardiac disease

E. Pulmonary disease

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F. Multiorgan failure
G. Fixed dilated pupil for prolonged periods
H. Cerebral perfusion pressure <40 mm Hg
I. Intracranial pressure >35 mm Hg. For than 1–2 hours

Relative Contraindications

A. More than 70 years
B. Infections under treatment
C. History of psychiatric problem
D. Rapidly increasing requirement for vasopressor support

Outcomes

A. Control of cachexia, portal venous collateral
B. Correction of coagulant defects by plasma derivatives and platelets
C. Within 3 months of surgery death is due to sepsis and neurological complications.
D. Survival rate is better in acute liver failure as compared to cirrhosis.

Q3. Pathophysiology, diagnostic approach, and management of Budd–Chiari syndrome.

PGI/NOV2013/MDIII (10)

Budd–Chiari syndrome.

KHUS/MAY2014/MDIII (10)

Anatomy of vascular system of liver. Management of Budd–Chiari syndrome.

ODISHA UNI, 2020 (10)

Vascular supply will be described in question number 28.

ANSWER

Budd first described this disease as triad of hepatomegaly, abdominal pain, and ascites and Chiari provided the pathological description of it. So, it can be defined as a potentially life-threatening disorder characterized by hepatic venous outflow obstruction manifested by abdominal pain, hepatomegaly, and ascites. Obstruction can arise from the site of efferent vein of the acinus to inferior vena cava prior to its drainage into right atrium.

Etiopathogenesis

A. Myeloproliferative disorders:
  a. Polycythemia rubra vera
  b. Essential thrombocytosis
  c. Idiopathic myelofibrosis
  d. Occult myeloproliferative disorders

  First three are called Philadelphia-negative myeloproliferative neoplasia. Last one can be diagnosed by erythroid bone marrow colony test. All are JAK2 positive.
B. Collagen vascular disease:
  a. Systemic lupus erythematosus
  b. Antiphospholipid syndrome
  c. Idiopathic granulomatous venulitis
C. Paroxysmal nocturnal hemoglobinuria
D. Other hypercoagulable state:
  a. Mutation of factor V Leiden
  b. Deficiency of antithrombin III
  c. Deficiency of protein S and C due to poor liver synthesis
  d. Oral contraceptive pregnancy
E. Trauma produces membrane obstruction to inferior vena cava.
F. Mechanical obstruction:
  a. Polycystic liver disease
G. Metastasis from tumor produces obstruction to inferior vena cava:
  a. Hepatocellular cancer
  b. Renal carcinoma
  c. Angiosarcoma
  d. Leiomyosarcoma
  e. Wilm's tumor
H. Systemic diseases:
  a. Sarcoidosis
  b. Inflammatory bowel disease (IBD)

Pathological changes include the following:

A. In acute case occlusion of inferior vena cava by thrombus—it may be purulent or fibrous strand. Site of block starts from hepatic venule to end of inferior vena cava prior to its entry to right atrium.
B. In acute stage:
  a. Liver is enlarged, smooth with venous congestion, cut surface shows "nutmeg," and in acute stage subcapsular lymphatics are prominent and dilated.
C. In chronic case:
  a. Enlarged caudate lobe compresses the inferior vena cava.
  b. Regenerative nodules after first hepatic vein thrombosis progress to involve portal venous system.

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c. Spleen is enlarged.
d. Mesenteric vessels will thrombose.

D. Histology demonstrated:
a. Zone 3 venous dilatation associated with hemorrhage and necrosis.
b. Hepatic venule obstruction leads to venocentric cirrhosis whereas, portal vein obstruction leads to venoportal cirrhosis.

Diagnosis

The diagnosis is composed of clinical features and different investigations.

Clinical Features

Clinical features depend upon:

A. Speed of occlusion
B. Site of obstruction
C. Severity of liver dysfunction

Spectrum of disease varies from severe fulminant form to chronic slow growing form or even asymptomatic.

In acute form:

A. Precipitating causes will continue and present according to the nature of the diseases, such as:
a. Polycythemia
b. Hepatocellular or renal carcinoma
c. Diarrhea
d. Liver enlargement
e. Watery diarrhea
B. In case total obstruction of hepatic vein:
a. Different grades of unconsciousness
b. Hepatocellular failure
c. Death

In chronic form:

A. Jaundice
B. Abdominal pain
C. Hepatomegaly mainly caudate lobe of liver in the epigastrium
D. Ascites
E. Splenomegaly
F. In case of inferior venacaval obstruction:
a. Edema
b. Venous distension over the flanks and back

Asymptomatic form: It occurs in 15% of patients. These patients demonstrate no ascites, hepatomegaly or splenomegaly or abdominal pain. These patient are usually diagnosed by accidental detection of abnormal liver function test.

Investigations

A. Liver function test:
a. Bilirubin rarely increases >2 mg/mL.
b. Alkaline phosphatase is reduced.
c. Albumin will be reduced due to liver failure of protein-losing enteropathy.
d. Transaminases level >1,000 IU/L suggests acute outflow obstruction or hepatocellular failure.
B. Prothrombin time is normal
C. Ascitic fluid protein is high 25 g/L
D. Radiology:
a. Ultrasound:
1. Shrunken liver with caudate lobe hypertrophy
2. Abnormalities of hepatic vein
3. In acute stage hyperechogenic but in later stage hyperechogenic with fibrosis
4. Presence of ascites
E. Doppler ultrasound:
a. Abnormalities of direction of flow of blood in hepatic vein and retrohepatic inferior vena cava.
b. Blood flow in inferior vena cava and hepatic vein will be absent, reversed or turbulent or continuous.
F. Color Doppler studies: It will detect abnormalities in hepatic veins, inferior vena cava, and portal vein.
G. CT scan of abdomen: It demonstrates:
a. Enlargement of liver with:
1. Diffuse hypodensity prior the contrast
2. Patchy enhancement but completely hypodense in case of complete obstruction of hepatic vein after contrast.
3. Caudate lobe is dense with surrounding under perfused parenchyma.
H. Magnetic resonance imaging (MRI):
a. Absence of normal hepatic venous drainage
b. Absence of normal inferior venacaval drainage
c. Alteration of signal intensity
d. Deformity of inferior vena cava by enlarged caudate lobe
I. Hepatic venography:
a. Narrowed hepatic veins
b. Tortuous, lace-like adjacent veins, pattern spider-web like signifying patent collaterals
J. Inferior venography:
a. In the hepatic segment, there is side-to-side narrowing of inferior vena cava.

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b. Pressure measurement of throughout the inferior vena cava to the uniform patency and any membranous obstruction or caudate lobe obstruction

K. Celiac angiography:

a. Branches of hepatic artery are stretched and displaced.

b. Multiplying space-occupying lesions in the liver looking like metastases

L. Liver biopsy:

a. Speckled zone 3 congestion

Treatment

A. Drug treatment:

a. In case of hypercoagulability—anticoagulation

b. In case of polycythemia and thrombocytosis—venesection or cytotoxic therapies

c. In case of PNH—molecular therapies, such as eculizumab.

d. Ascites—low sodium in the diet, diuretics

B. Percutaneous transluminal angioplasty:

a. After liver transplantation to dilate the web and narrowing of inferior vena cava this procedure is of choice in case of suprahepatic portion of inferior vena cava.

b. In case of hepatic vein multiple dilatation followed by administration of metallic stent. This should be tried in case of failed angioplasty.

C. Transjugular intrahepatic stent shunt: It should be done in case of failed anticoagulation and percutaneous angioplasty.

Aim is:

a. Decompression of liver

b. There is reversal of portal venous flow.

c. In case of acute state it will rescue the patients where emergency transplantation cannot be done.

It will avoid:

a. Open surgery

b. Mortality

In case where hepatic vein cannot be entered the approach should be transcaval.

D. Surgical portosystemic shunt:

Indications:

a. Liver transplantation is not feasible

b. TIPS are not available

Contraindications:

a. Acute Budd–Chiari syndrome as here salvage transplantation is required in case of liver failure.

b. In case of portal venous obstruction

Prognosis: 5-year survival rate is 87% but it will be reduced to 38% in case of shunt thrombosis.

Anticoagulation is required throughout the life.

If the pressure in the infrahepatic portion of inferior vena cava exceeds 20 mm Hg due to pressure of enlarged caudate lobe, venacaval stenting has to be done first followed by shunting.

Type of shunt: Interposition mesocaval graft as it will not affect the subsequent hepatic transplantation. If inferior vena cava is obstructed Mesoatrial shunt is used.

E. Liver transplantation:

Indications:

a. In case of progression to cirrhosis with hepatocellular failure

b. In case of deterioration in spite of medical and radiological treatment

But TIPS should be done as a stop-gap step so that more time will be present for procuring the donor-liver.

If the underlying is hypercoagulability then life-long anticoagulation has to be given.

One year and 5-year survival rates are 85% and 80%, respectively.

Q4. Discuss the management of hepatic encephalopathy.

BF/NOV2013/MDIII (10)

Hepatic encephalopathy.

MGR/MA2006/MDI (5)

Precipitating factors and management of hepatic encephalopathy.

MGR/FEB2005/MDI (5)

Clinical features and management of hepatic encephalopathy.

RGUHS/SEP2002/MDII (10)

West Haven classification of hepatic encephalopathy.

DNB (2020) (4)

Hepatic encephalopathy.

KERALA UNI, 2021 (10)

BHARATI VIDYAPEETH DEEMED UNI, JHELUM (10)

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Acute hepatic encephalopathy.
MAHARASHTRA UNI OF HEALTH SC, VIJAYAWADA, 2020 (10)

Hepatic encephalopathy.
MGU, 2024 (5)

Hepatic encephalopathy and its management.
RAJASTHAN UNIVERSITY, 2023, (8)

ANSWER

Hepatic encephalopathy is a reversible metabolic encephalopathy occurred as a consequence of advanced hepatic failure due to various etiologies. If the inciting events are not treated successfully the survival of the patients will be shortened.

Though ammonia level in the blood is high in patient with hepatic encephalopathy but there is lack of correlation between the two which means that factors other than ammonia may come into play in the development of hepatic encephalopathy.

Precipitating Factors

Ammonia:

A. In the gastrointestinal tract:
  a. In the small intestine ammonia is produced through the deamination of glutamine via deaminase.
  b. In the large intestine through the bacterial degradation of urea and proteins.

B. Kidney produces small amount of ammonia which is aggravated by treatment with diuretics and in hypokalemia.

C. In liver disease in the state of sarcopenia glutamine is also released from the muscles.

Normally, ammonia enters into the liver and is converted to urea through urea cycle which will be ultimately cleared by kidney. But in case of cirrhosis with portosystemic shunting ammonia will bypass the liver thus increasing its concentration in the blood and it crosses the blood–brain barrier into brain where astrocytes will convert ammonia and glutamate into glutamine by glutamine synthetase. Glutamine will be accumulated in the astrocytes and it will draw water as it is osmotically active leading the swelling of these cells. Glutamine also enters mitochondria and is cleaved into ammonia and glutamate by glutaminase leading to increased concentration of ammonia in the cells which is responsible for "Feed forward loop"—according to it increased intracellular ammonia concentration leads to production of reactive oxygen and also nitrogen species perpetuating further edema.

In case of long-standing exposure of brain to ammonia myo-inositol and taurine will be released from the brain cells leading to lowering of myo-inositol in the cells producing decompensated hepatic encephalopathy.

Cerebral perfusion will be altered in hyperammonemia leading to redistribution of cerebral blood flow to subcortical areas from cerebral cortex which produces impaired neuropsychiatric performances.

Effect of inflammation:

Inflammation occurs in following conditions: (1) Sepsis, (2) Acute liver failure, (3) Cirrhosis, (4) Obesity, (5) Gastrointestinal bleeding, and (6) Alteration of gastrointestinal microbiota. As a result proinflammatory cytokines, tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and IL-6 are released which alter the morphology of astrocytes leading to increased permeability of blood–brain barrier.

Effect of microbiota:

A. There is release of ammonia, indoles, oxindoles, and endotoxins leading to cognitive impairment.

B. In case of cirrhosis, in case dysbiosis, there is reduced level of members of autochthonous taxa, such as Clostridiales, Ruminococcaceae, and Lachnospiraceae and increased level of Streptococcaceae and Enterobacteriaceae. In hepatic encephalopathy, there is endotoxemia and lower dysbiosis rate and this endotoxemia activates immune response and inflammatory cascade leading to liver damage as well as augmentation of cerebral edema.

Neuromodulators:

A. Gamma-aminobutyric acid (GABA): Increase sensitivity of benzodiazepine receptors on astrocytes will activate GABA system increasing the tone of GABAergic tone in the brain

B. Excess benzodiazepine like compounds derived from vegetable diet, intestinal flora, and medications contribute to hepatic encephalopathy.

C. Ammonia binds to GAB receptor presents on the astrocytes triggering neurosteroid synthesis

D. Serotonin

E. Acetylcholine

F. Monoamines

G. Glutamate

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Manganese deposition: Usually manganese is excreted in bile from the liver. But in case of cirrhosis with portosystemic shunting manganese leading to increased blood level and deposition of manganese in the brain augmenting hepatic encephalopathy.

Clinical Features of Hepatic Encephalopathy

There is wide spectrum of mental changes from near normal which can be diagnosed by specialized testing to extremes of mental changes. This hepatic encephalopathy is of following types:

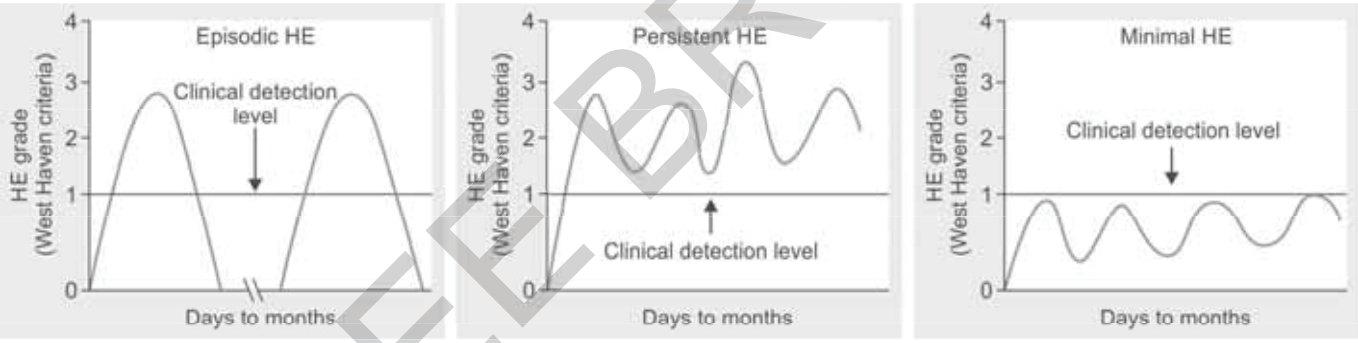
Type	Definitions	Grade	Term	Course	Spontaneous or not
A	Hepatic encephalopathy associated with acute liver failure	Minimal change	Covert hepatic encephalopathy	Episodic	Spontaneous
B	Hepatic encephalopathy associated with portosystemic bypass and no acute liver failure	2	Overt hepatic encephalopathy	Recurrent	Precipitated
		3			
C	Hepatic encephalopathy associated with cirrhosis or portal hypertension/portosystemic shunt	4		Persistent	

In case of minimal changes: Encephalopathic changes are always below clinical detection level, hence this type of covert in hepatic encephalopathy can be diagnosed by specialized testing.

Overt encephalopathy may be of two types:

A. Persistent encephalopathy: In it mental changes are always above the clinical detection level with minimal fluctuation.

B. Episodic encephalopathy: In this condition neurological changes are episodic with upper limit and are always above the clinical detection level but in between the episode the patient will be completely normal.



(HE: hepatic encephalopathy)

Different modalities of sensations in patients with different types of encephalopathies:

Tests	Functions	CHE	OHE	Late OHE
Psychomotor	Normal	Abnormal	Abnormal	Not done
Neurophysiologic	Normal	Abnormal	Abnormal	Not done
Clinical	Normal	Normal	Abnormal	Abnormal

(CHE: covert hepatic encephalopathy; OHE: overt hepatic encephalopathy)

Clinical classifications of hepatic encephalopathy are based on West Haven criteria:

Grade	Features
0	No abnormality detected
1	Euphoria, anxiety, trivial loss of awareness, impairment of addition or subtraction, and attention span is shortened
2	Lethargy, disorientation of time, apathy, personality changes, and inappropriate behavior
3	Somnolence to stupor, confused, response to stimuli will be lowered, gross disorientation, confused, and bizarre behavior
4	Coma

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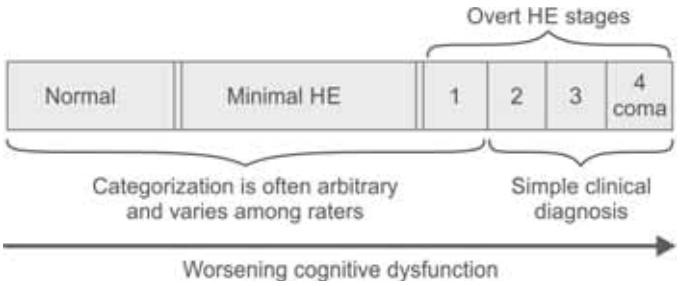

(HE: hepatic encephalopathy)

Physical signs:
In case of overt hepatic encephalopathy:

- **a.** Hyperreflexia
- **b.** Positive Babinski sign
- **c.** Asterixis: It occurs due to disturbance in oscillatory network of the brain. It is shown in upper and lower extremities and tongue.

Management of Hepatic Encephalopathy

A. Correction of precipitating factors:

- **a.** Increased load of nitrogen occurred from gastrointestinal bleeding, infections, and increased dietary protein
- **b.** Toxin clearance will be reduced as a result of constipation, renal failure, portosystemic shunt, acute on chronic liver failure, and noncompliant medication
- **c.** Neurotransmission will be altered due to hypoglycemia, hypoxia, sedation, and alcohol intoxication.

More than 80% patients will be recovered after correction of the above precipitating factors. Patients with grade III encephalopathy will be treated in intensive care unit as there is facility of mechanical ventilation.

Medical Therapy in Case of Overt and Persistent Hepatic Encephalopathy

It includes the management of episodic hepatic encephalopathy and persistent hepatic encephalopathy and this should be followed by prevention of secondary hepatic encephalopathy. With the first line of therapy if the patient responds within 24–48 hours it will support the diagnosis, but if the patient will not respond for >72 hours then other cause of altered mentation has to be sought.

Nonabsorbable disaccharides: These are lactulose and lactitol.

Mechanism of actions: In the colon lactulose will be converted to acetic acid and lactic acid and colonic pH will be reduced. In low pH survival of urease-producing bacteria will be decreased thereby facilitating the conversion of ammonia to less readily absorbable ammonium. It will act as cathartic to increase excretion of the nitrogenous waste.

Adverse effect: Cramping abdominal pain, diarrhea which may be so severe that patient develop hypovolemia and dehydration and electrolyte imbalance.

Dose:

A. Initial dose is 20–30 mL twice daily to maintain two semisolid stool per day, this followed by dose should be adjusted according to the patients. This drug has to be continued indefinitely in patient with persistent hepatic encephalopathy.

B. In case of comatose patients this drug has to be administered as 300 mL in 1 L of water every 6–8 hours till the patient will initiate oral intake.

Antibiotics: The drug is rifaximin, neomycin, and metronidazole.

Mechanism of action of rifaximin: It will change the microbiota in the gut and create more favorable microbiome so that endogenous ammonia production by bacteria will be reduced. It is active against gram-positive, gram-negative anaerobic bacteria. This drug will not be absorbed systematically.

Dose: 550 mg thrice daily

Mechanism of action of neomycin: It will inhibit the activity of glutaminase which will convert glutamine to glutamate and ammonia thus prevent the formation of ammonia.

Dose: Orally 1–4 g daily in divided doses

Adverse effects: Nephrotoxicity and ototoxicity—for these complications this drug is not used now.

Mechanism of actions of metronidazole: It acts against gram-negative anaerobic bacteria in the gut which will hydrolyze urea to ammonia leading to decreased formation of ammonia.

Dose: 400 mg twice daily orally

Toxicity: Abdominal cramps, metallic taste. Long-term use may lead to potential toxicity.

Nutrition: Most of these patients may suffer from severe protein energy malnutrition. The patient with overt encephalopathy usually requires 35–40 kcal/kg in addition to small nutritional supplements throughout the day.

Protein intake: In this patient no restriction of protein intake should be advised because skeletal muscles metabolize ammonia. Daily requirement is 1.2–1.5 g/kg/day.

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Nonabsorbable vegetable fiber: It should be taken in large amount to increase clearance of nitrogenous waste via stool.

Branched chain amino acid (BCAA): Cirrhotic patients have altered ratio of amino acids with increase in aromatic amino acid (AAA) as compared to BCAA leading to development of encephalopathy by changing the cerebral neurotransmitter balance. Orally BCAA alters the ratio and is effective in patients with hepatic encephalopathy who are not responding to oral lactulose and rifaximin.

Leucine stimulates the production of hepatocyte growth factor with the help of stellate cells leading to regeneration of hepatocytes and thus compensate death of liver cells.

L-ornithine L-aspartate (LOLA): It improves the patient with encephalopathy and LOLA will reverse the ratio of AAA to BCAA and thus lowering the amount of ammonia.

Dose: 6 g thrice daily orally in grade II encephalopathy. Since aspartate moiety will undergo transamination in the gut mucosa hence, the efficacy of this drug depends upon the ornithine moiety alone.

Zinc: It is a cofactor for urea cycle enzyme and ammonia detoxification by reducing the activity of glutathione synthetase. Its level is commonly low in patients with cirrhosis. So, zinc supplementation commonly helps the patient from intoxication of ammonia.

Bromocriptine: These patients have deficit in dopaminergic neurotransmission. So, chronic stable persistent hepatic encephalopathy having extrapyramidal features which are resistant to previous agent can respond to this dopamine agonist bromocriptine.

Dose: 2.5 mg daily to maximum 5 mg twice daily.

Complication: Ototoxicity. So, every 6 month audiogram should be done in this patient.

Flumazenil: In patient with hepatic encephalopathy has

A. Deficit in GABAergic neurotransmission.

B. Increased level of circulating benzodiazepine like ligands.

This drug is benzodiazepine receptor antagonist, thus when given intravenously it will improve the encephalopathy for a short time.

Surgical Therapy

Shunt Occlusion

Spontaneous or artificial shunt, like TIPS, may be responsible for persistent hepatic encephalopathy which may be difficult to treat. So these shunt should be occluded to prevent or worsen the encephalopathy. The methods included are:

A. Vascular embolization

B. Vascular plugging with Amplatzer device

C. Balloon occlusion

D. Laparoscopic disconnection of periumbilical vein shunt.

Liver Transplantation

Model for End-stage Liver Disease (MELD) is used to prioritize the patient for liver transplant. This scoring system does not include neuropsychiatric status. Now selection of the patients is based on presence of hepatic encephalopathy with preservation of liver function test with exclusion of other types of neuropsychiatric manifestation.

Postliver transplant patient shows following improvement:

A. Parkinsonian features resistant to treatment

B. Resolution of electroencephalography, cerebral MRI, cerebral positron emission tomography (PET)

C. Improvement of cognitive functions

These patients may also unmask following effects:

A. Preexisting unrecognized abnormalities

B. Effects of immunosuppressive therapy

C. Effect of comorbidities, like systemic hypertension

D. Development of neurological complications.

Artificial liver support system: Patients with severe encephalopathy having decompensated cirrhosis who do not respond to conventional therapy may require support.

A. To provide time during which the inciting event may be corrected

B. It acts as a bridge for future liver transplantation.

Most extensively studied liver support is Molecular Adsorption Recirculating System (MARS). It removes both lipophilic albumin-bound as well as water-soluble molecules and thus purifies blood. Thus it will improve cerebral hemodynamics by removing:

A. Circulating ammonia

B. Endotoxin

C. Inflammatory mediators

Colectomy/Colonic exclusion: It will reduce intestinal production of ammonia. But operative morbidity and mortality is very high.

Future Therapies

Hepatic encephalopathy is mainly based on increased production and decreased excretion of ammonia. So, treatment should be based on:

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A. Prevention of ammonia production in the intestine: Enterocytes breakdown glutamine after its uptake from the intestine. Phosphate activated glutaminase (PAG) is responsible for catabolizing the glutamine to produce ammonia. Concentration of PAG is about four times higher in duodenum in cirrhotic patients. So, inhibitors of this PAG may reduce the blood ammonia level and provide therapeutic benefit.

B. Kidney is the organ where ammonia is produced and excreted. In cirrhotic patient expansion of plasma leads to excretion of ammonia.

C. Skeletal muscle cells detoxify ammonia by converting it to glutamine by glutamine synthetase which is promoted by ornithine and phenylacetate promotes excretion of this glutamine through kidney.

Recently newer pathogenic and potentially harmful agents are recognized and possible potentially alternative treatments are:

A. *L-carnitine:*

It is used:

a. In children having urea-cycle deficiency with hyperammonemia

b. Valproic acid-induced hyperammonemia

Mechanism of actions:

a. It acts on metabotropic glutamate receptors at the level of brain in ammonia uptake.

b. It acts on mitochondrial metabolism.

B. *Rivastigmine*:

Mechanism of action: In cirrhotic patient with hepatic encephalopathy acetylcholine is considerably low. This drug inhibits reversibly cholinesterase and thus improves the psychomotor performance in this patient.

C. *Endocannabinoids*:

Mechanism of action: In patient with hepatic encephalopathy neural intoxication disrupts cerebral energy flux. This drug augments the adenosine monophosphate (AMP)-activated protein kinase and thus improves the cellular energy store in response to metabolic injury.

D. *Sildenafil*:

Mechanism of action: In hepatic encephalopathy altered function of glutamate-nitric oxide-cyclic guanosine monophosphate (cGMP) pathway and decrease in extracellular cGMP in the brain lead to cognitive function decline. This drug modulates cGMP concentration thus restoring the learning episode. This is under phase III trial.

E. *Metabotropic glutamate receptors 1 (mGluR1)*:

Mechanism of action: In the pars reticulata of the substantia nigra of this patient there is alteration of glutamatergic neurotransmission leading to psychomotor slowing. This drug blocks the mGluR1 receptor and thus normalizes the brain activity. This is in phase III trial.

Q5. Bilirubin metabolism and outline of diagnostic approach to a patient with hyperbilirubinemia.

PGI/APR2013/MDI (10)

Bilirubin metabolism, classify hyperbilirubinemia syndrome, outline approach to diagnosis.

DNBIV/JUN2011 (10)

Bile pigment metabolism.

MGR/OCT2012/MDI (5)

Congenital hyperbilirubinemia.

MGR/OCT2003/MDIII (10)

Jaundice.

MGR/MAR2008/MDI (5)

Write bilirubin metabolism and causes of portal hypertension.

ODISHA UNI, 2021 (10)

Briefly describe bilirubin metabolism. How do you classify jaundice? Outline the clinicopathological approach to a case of jaundice.

BHARATI VIDYAPEETH DEEMED UNIVERSITY, 2019 (15)

Outline the bilirubin metabolism and describe the histopathology of chronic viral hepatitis.

AIIMS (BHU), 2024 (10)

Bilirubin metabolism.

MANIPUR UNIVERSITY, 2018 (10)

Histological changes in chronic viral hepatitis has been described in question number 35.

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ANSWER

Bilirubin Metabolism

Bilirubin is derived mainly from hemoglobin but small fractions also derived from myoglobin, cytochrome 450, and immature bone marrow cells. Nearly daily 300 mg of bilirubin is formed. In the reticuloendothelial system the enzyme hem oxygenase breaks hemoglobin at α-methane bridge porphyrin ring to globin, hem, biliverdin, and carbon monoxide. This biliverdin will be at once converted into bilirubin by biliverdin reductase, a cytosolic enzyme. This bilirubin due to its water insolubility is bound to albumin and transported into plasma. Bilirubin is transported from the blood into bile through four distinct steps:

A. Hepatocellular uptake: This albumin bound bilirubin in the sinusoidal blood reaches the surface of hepatocytes through the endothelial cell fenestrae. Then bilirubin is removed from albumin and enters into the hepatocytes by two processes, one is facilitated diffusion and second is by simple diffusion.

B. Intracellular binding: Within the hepatocyte bilirubin binds to cytosolic carrier protein glutathione-S-transferase, called ligandin.

C. Conjugation of bilirubin: Bilirubin will be conjugated with one and two glucuronic acids to monoglucuronide and diglucuronide, respectively with the help of UDP-glucuronosyltransferase thus by disrupting the internal hydrogen bonding making it highly soluble in water. Major bilirubin conjugate is diglucuronide but sulfate, xylose glucose conjugation may occur.

D. Biliary excretion: Conjugated bile is excreted across the canalicular membrane into bile by ATP-dependent multidrug resistance-associated protein 2 (MRP2). Some amount of conjugated bilirubin is secreted into portal circulation with the help of MRP3 which will be taken back into hepatocyte by sinusoidal uptake transporter, organ anion transport protein 1B1 (OATP 1B1).

Extrahepatic Aspect of Bilirubin Metabolism

After the secretion of bile into bile it will reach into duodenum and from there it will pass down the gastrointestinal tract without its reabsorption through the mucosa.

In the gut through bacterial β-glucuronidase and other enzymes large fraction will be converted into water-soluble colorless compound urobilinogen. Most of the urobilinogen will be converted into stercobilinogen and excreted in stool.

Rest of urobilinogen undergoes enterohepatic cycling. Urobilinogen that enters into the hepatocytes will reach systemic circulation and will be excreted through kidney. If urobilinogen excretion in urine is increased it indicates high plasma level—it may be due to overproduction of urobilinogen or decreased hepatic clearance of it.

Classification of Hyperbilirubinemia

A. Disorders associated with unconjugated hyperbilirubinemia (>85% of total):
- **a.** Physiological jaundice of newborn
- **b.** Hemolysis
- **c.** Resorption of hematoma
- **d.** Ineffective erythropoiesis:
  - Thalassemia
  - Megaloblastic anemia
- **e.** Maternal milk jaundice
- **f.** Congenital diseases:
  - Gilbert's syndrome
  - Crigler–Najjar syndrome I and II

B. Predominantly conjugated hyperbilirubinemia:
- **a.** Hepatitis
- **b.** Cirrhosis
- **c.** Cholelithiasis
- **d.** Toxins
- **e.** Drugs:
  - Anabolic steroid
  - Oral contraceptive pills
- **f.** Congenital:
  - Dubin–Johnson syndrome
  - Rotor syndrome
  - Benign intrahepatic cholestasis
  - Progressive familial intrahepatic cholestasis (PFIC)

C. Mixed (unconjugated and unconjugated) hyperbilirubinemia (conjugated 20–25% of total):
- **a.** Viral hepatitis
- **b.** Alcoholic hepatitis

Congenital Hyperbilirubinemia

Gilbert Syndrome

A. It is autosomal recessive disease; it occurs in 5% of the population.

B. Bilirubin level is never above 5–8 mg/dL.

C. Routine liver function test is normal.

D. Serum bile acid is normal.

E. Liver histology is normal.

F. Oral cholecystography is normal.

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