Hepatic Encephalopathy

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Definition

- Complex neuropsychatric syndrome complicating advanced liver disease and/or portosystemic shunting (1990s)
- Complex neuropsychatric syndrome caused by portosystemic venous shunting with or without intrinsic liver disease (M C North Am 2008)
- Complex neuropsychatric syndrome complicating acute and chronic liver failure (Schliess etal 2009)

Pathogenesis

- The pathogenesis of HE remains poorly understood (WJ Gastroenterol 2008)

- HE in liver cirrhosis is a clinical manifestation of a low-grade cerebral edema, which is exacerbated in response to ammonia and other neurotoxins (Haussinger D et al, 2008)

- The accumulation of ammonia and other neurotoxins in the systemic circulation is the main pathogenic factor in HE.

- Normally, these neurotoxins are produced (gut bacteria) and absorbed from the gut and cleared by the liver.

- When liver function is seriously impaired (Acute or Chronic LF), these neurotoxins bypass the liver and gain access to the systemic circulation, cross the blood-brain barrier, and accumulate in the CNS.

- Unchanged ammonia traverses the BBB, and enter the parenchymal cells (especially astrocytes), where it is converted into glutamine.

- Glutamine in turn has osmolar activity and increases the cell water content, contributing to cerebral edema.

- Therefore, ammonia plays the key role in the pathogenesis of HE by inducing astrocyte swelling and/or sensitizing astrocytes to swelling by a heterogeneous panel of precipitating factors and conditions (Chleiss F et al 2009)

- Whereas astrocyte swelling is so marked in ALF and leads to clinically overt brain edema, a low grade glial edema without clinically overt brain edema is observed in HE complicating liver cirrhosis (Chronic LCF).

- This overt brain edema in ALF may lead to increased intracranial pressure and potentially, brain herniation.

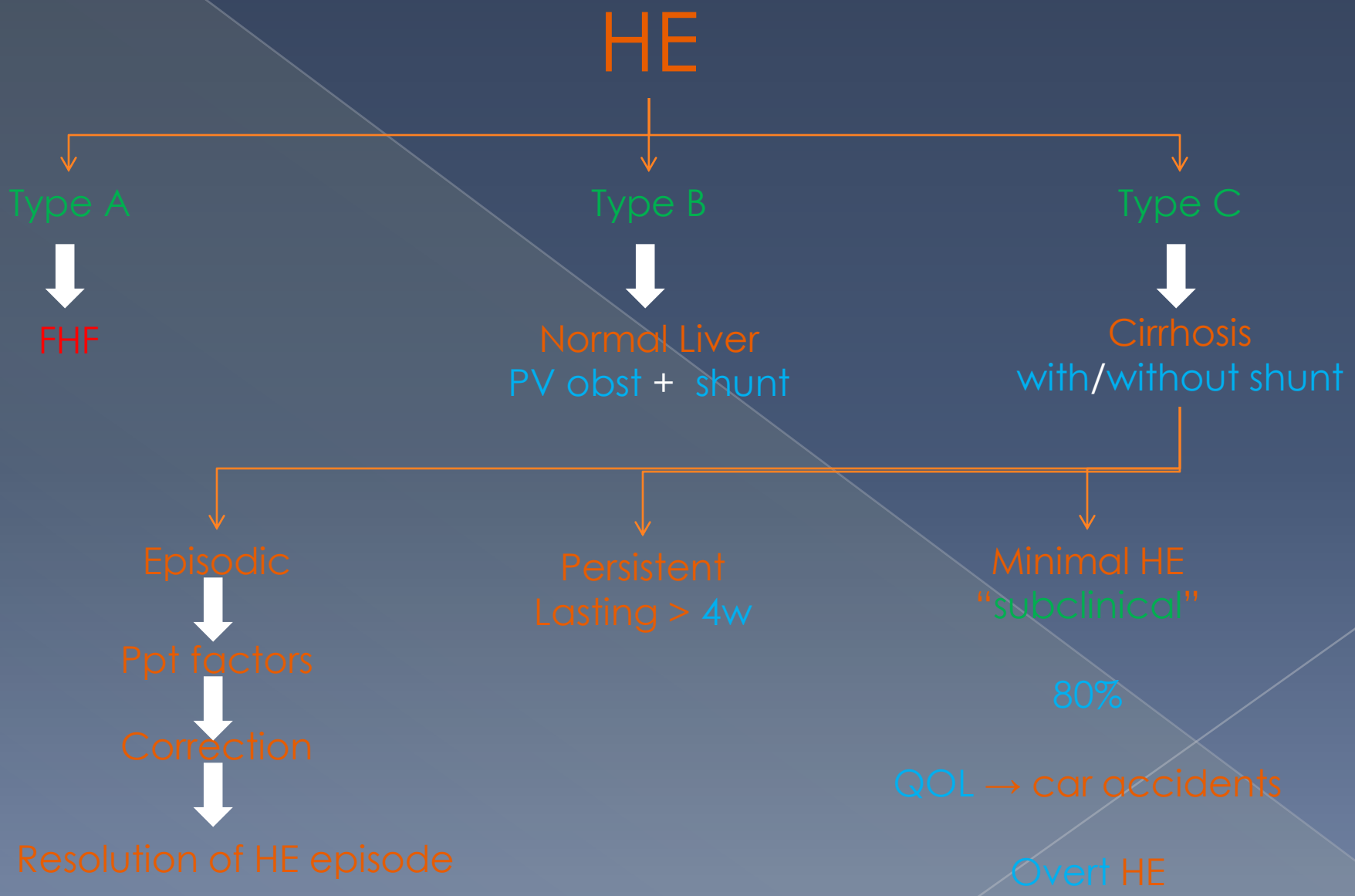
- Swelling of astrocytes produces reactive oxygen and nitrogen oxide species (ROS/RNOS), which again increases astrocyte swelling and subsequently induces RNA oxidation that may impair postsynaptic protein synthesis, which is required for memory formation and offers a novel explanation for multiple disturbances of the neurotransmitter systems, gene expression, motor and cognitive deficits observed in HE

(Schliess et al 2009)

Clinical significance and Magnitude of the problem

- About 1/3 to ½ of hospitalizations for cirrhosis are related to HE
- Patients with HE often have other manifestations of ESLD, however HE can also develop as an isolated manifestation of decompensated cirrhosis.
- Hepatic encephalopathy may disable the patient from employment, driving and self care.
- HE usually signals advanced liver disease and consequently is often considered a clinical indication for liver transplantation

Types of hepatic encephalopathy



PPT factors for HE

- GI bleeding
- Infections: (SBP, UTI, chest, skin)
- Constipation
- Excessive dietary proteins
- Electrolyte disturbance: (Hypokalemia, Hyponatremia)
- Superimposed liver injury: (acute viral hepatitis, drugs)
- Surgery
- CNS depressant drugs
- HCC
- Dehydration
- Renal failure
- TIPS

Clinical staging of HE

(MCNA 2008)

- An objective, simple, specific and sensitive method to diagnose the severity of HE has not yet been devised

Grade	Findings
Grade 0 MHE	✓Subclinical. ✓No abnormality
Grade I Mild	➢Inverted sleep pattern ➢Shortened attention span ➢Impaired addition and subtraction ➢Euphoria, depression, irritability ➢Impaired handwriting (incoordination)
Grade II Moderate	✓Lethargy, intermittent disorientation (time) ✓ Personality changes ✓ Asterexis (flapping)
Grade III Severe	➢Slurred speech ➢Somnolence, semistupor ➢Complete disorientation (time, place) ➢Paranoia + bizarre behavior ➢↑ reflexes + babiniski's sign
Grade IV Coma	With or without response to stimuli

Diagnosis & differential diagnosis

- Suspect in any liver disease patient presenting with mental changes ?
- HE is usually preceeded by ppt factor
- Asterexis = flapping tremors
  - Stage II
  - Weakens in stage III
  - Disappears in coma

- Seizures and focal neurological signs are uncommon manifestation of HE ➔ warrants appropriate brain imaging ➔ Structural brain damage ➔ Subdural hematoma !

Major differential diagnoses in HE

- Other metabolic encephalopathies:
  - Uremic
  - Hypoglycemia
  - Ketoacidosis
  - Hypoxia
  - Thyroid dysfunction
- CNS infections (meningitis, encephalitis)
- Ischemic brain disease (TIAs, Ischemic strokes)
- CNS tumors

Investigations

- Overt HE from history and clinical examination

- Diagnosis not clear or in question ?
  - Blood ammonia level
  - Brain imaging (CT, MRI)
  - EEG
  - Psychometric tests (MHE)

Blood ammonia

- Previously, discrepancy between blood ammonia level and severity of HE
- Currently; properly processed blood ammonia levels correlate well with the severity of HE

Problems in biochemical assay of ammonia:

- Labile ➔ spontaneous determination + evapouration at room temp
- Venous blood ammonia correlates well with arterial ammonia when properly assessed
- Samples must be withdrawn in heparinized container, placed in ice and assayed within 30 min

Concerns

- Normal blood ammonia level doesn't support the diagnosis of HE
- Conversely, an elevated ammonia level in a comatosed patient doesn't execlude a coexistent condition
- However, markedly elevated blood ammonia (> 150 – 200 umol/l) ➔ strongly suspicious of HE
- Blood ammonia is moderately elevated in cirrhotics without HE

Management

- PPT factors:
  - Dehydration
  - GIB
  - Infection
  - Electrolyte disturbance
    - Hypokalemia
    - Hyponatremia
- Artificial liver support
- Ammonia
  - ↓ production + absorption
    - Diet
    - Lactulose + lactitol
    - Oral antibiotics
  - ↑ ammonia clearance
    - L ornithine – L – Aspartate
- Liver transplantation

A) PPT factors

- Dehydration:
  - Stop diuretics
  - IV physiologic saline

A) PPT factors

- GI bleeding:

A) PPT factors

- Infection
  - SBP
  - UT
  - Chest

A) PPT factors

- Electrolyte disturbance
  - Hypokalemia → IV k
  - Hyponatremia → hypertonic saline

(150 ml of 3% NaCl IV)

(S. sodium < 125 mEq/L)

- Any episode of HE is considered due to ESLD only after execlusion of any ppt factor

B) Ammonia

There can be little doubt that ammonia, by both direct and indirect mechanisms plays the major role in the pathogenesis of HE in both acute and chronic LF

◉↓ Prodcution of gut ammonia

› Diet

- Excessive dietary protein can ppt HE
- Patients with compensated cirrhosis:
  - No restriction
  - Diet containing 1.2 gm protein/kg/ day is recommended

(MCNA, 2008)

- HE episode →

  - Protein restriction to 40 gm/ day is advocated not more than 48 hours and then minimized

  - Prolonged protein restriction in HE → can exacerbate the catabolic state of cirrhosis → release of AA and other nitrogenated byproducts from the muscles

  - Cordoba et al, 2004: found no difference in the improvement of the mental functions in 2 groups of patients with severe HE treated with low and high protein diet

Chronic HE

- Vegetable proteins are better tolerated than animal proteins:
  - ✓↑ content of dietary fibers → natural cathartic
  - ✓↓ levels of AA acids→ false transmitters
- Supplementation with oral branched chain AAs → improves survival and QOL (expensive)

(Mesejo et al, 2008)

Lactulose or lactitol (cathartics)

- Lactulose (beta – galactosido fructose)
- Lactitol (beta – galactosido sorbitol)

Lactulose & lactitol

Non absorbable disaccharides

Cathartic

↓ colonic bacterial load

Degradation by gut bacteria

Lactic acid + other organic A

Acidification of gut lumen

Inhibit ammoniagenic coliform bacteria

↓ Gut ammonia production

Dose

Orally

30 ml/2-4 times/day

(stage I, II)

3 – 5 loose motions

Enema or NGT

300 ml + 700ml tap water / 4h

(stage III, IV = coma)

(massive ascites)

- Many clinical trials demonstrated the efficacy of lacutlose in the treatment of HE (Dozen)

- However, one recent metanalysis contradicts these trials and forces the use of antibiotics particularly rifaxmin (BMJ, 2004)

Oral antibiotics

They ↓ the concentration of ammoniagenic bacteria → ↓ production of ammonia and other gut derived neurotoxins

- Neomycin →250 mg/ 2-4 times/ day
  - Its efficacy is ambigous (MCNA, 2008)
  - Long term therapy → toxicity due to some systemic absorption
- Metronidazole + oral Vancomycin are little studied

- Rifaximin (xifaxan)
  - non absorbable derivative of rifampin
  - 400 mg orally 3TD
  - Study from Texas 2008 have demonstrated that rifaximin showed superior efficacy compared with lactulose and neomycin in HE as well as better tolerability than both drugs due to minimal absorption
  - Concerns → cost ?

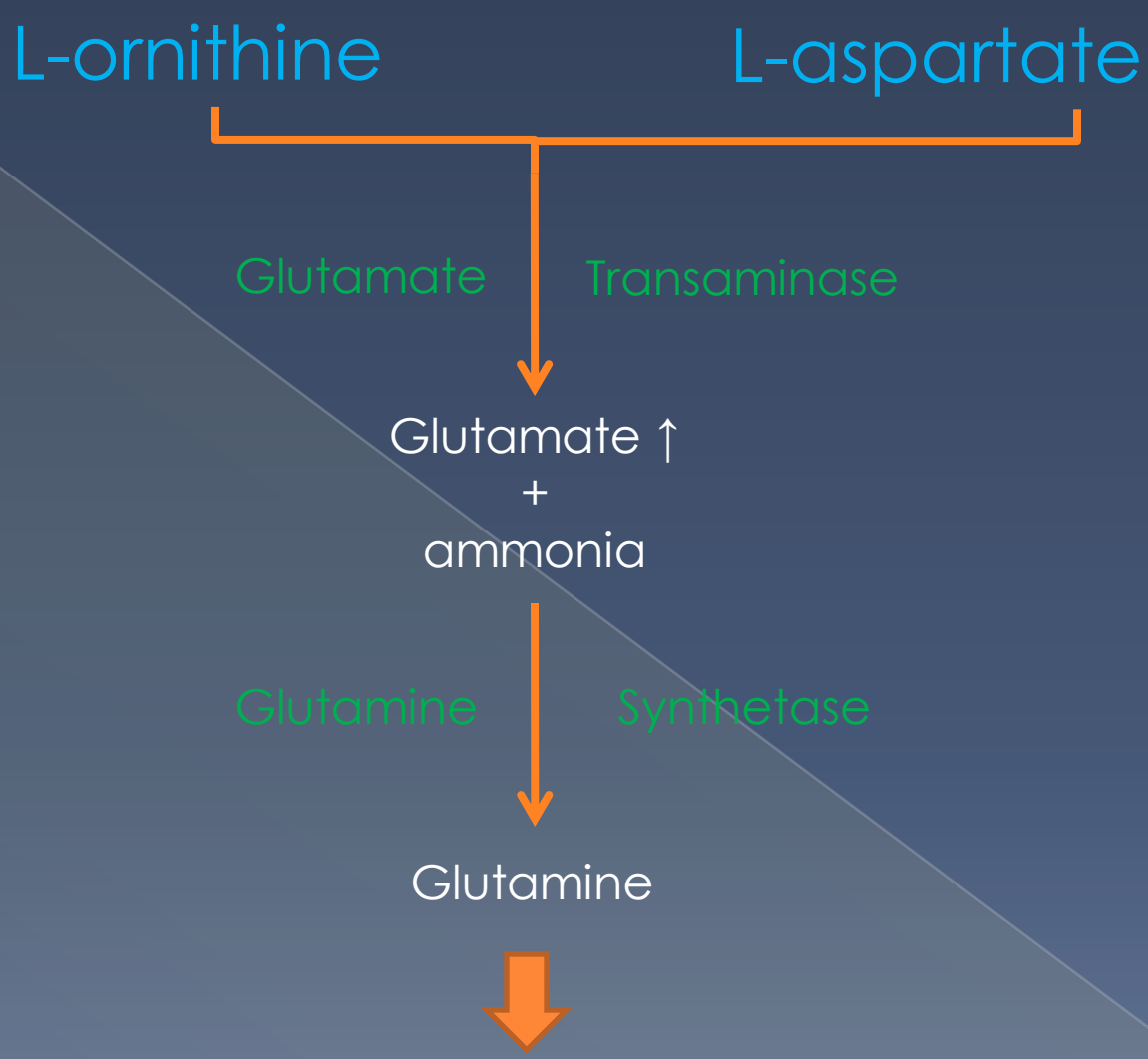
↑ammonia clearance

L-ornithine – L-aspartate (LOLA)

(Hepa- Merz, Merz Pharm-GMBH, Frankfurt Main, Germany)

- Stable salt of 2 amino acids:
  - L-ornithine
  - L-aspartate
- Dose: 20 gm/day/ in 250 ml of 5% dextrose water / IV infusion / 4Hs/ 5 consecutive days

(Ahmed et al 2008)


L-ornithine
L-aspartate
Glutamate
Transaminase
Glutamate ↑
+
ammonia
Glutamine
Synthetase
Glutamine
↑ clearance of ammonia

Several clinical trials

- Kircheis et al (Hepatology, 1997)
- Deleker et al (Hepatology, 2000)
- Ahmad et al (Jcoll physisians surg pak, 2008)

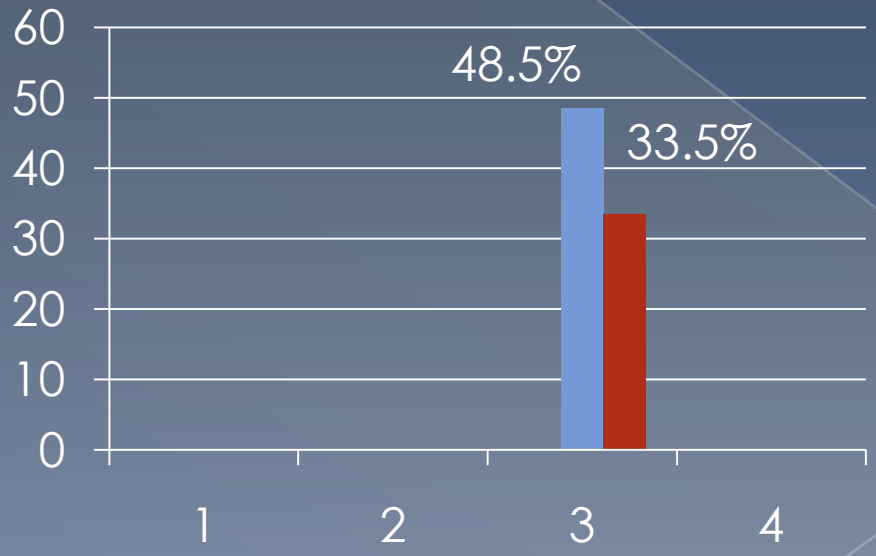
LOLA is effective in treating HE in cirrhotic patients

Role of artificial liver supports in HE "Liver dialysis"

- 2 systems:
  - MARS:
    - molecular adsorbent recirculating system
    - Albumin dialysis (AD 1999)
  - Prometheus: Fractoinated plasma separation (FDPS)
    - Intorduced 2003

Both systems are capable of removing both water solved and albumin bound toxins without providing synthetic functions

- Several clinical trials have shown that artificial liver support, is able to improve HE in acute and acute on chronic liver fialure
  - Stadlbeur et al, 2008 (Metab brain Dis)
  - Krisper et al, 2005 (Hepatology)
  - Faenza et al, 2008 (Transplant Procedure)



- Hassanein, T et al, 2007 (Hepatology)

  MARS + Medical Vs Medical therapy 5 days in stage III, IV HE

  Given complexity and cost, more evaluation is needed before adding this modality to the therapeutic bundle of HE

Liver transplantation

- Cirrhotic patients who develop severe HE have poor survival even with a fairly low MEID score, therefore, this constitutes a clinical indication for liver transplant evaluation

- is the only mode of therapy that tackles the real cause of chronic HE which is the lack of functioning hepatocytes

THANK

YOU