

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



Management of Hepatic Encephalopathy

By

Dr. El-Sayed Abdel-Maksoud Khalil

Principals of treatment

- * Reduction of production of ammonia
 - * Dietary protein restriction.
 - * Inhibition of urease producing colonic bacteria
- * Increased metabolism of ammonia in the tissues (Fixation of ammonia).
- * Reduction of false neurotransmitters.
- * Inhibition of GABA benzodiazepine receptors.
- * Correction of manganese deposition in basal ganglia.
- * Dopaminergic drugs.
- * Opiate receptor agonist.
- * Liver transplantation.

Dietary protein restriction

Patients with cirrhosis often require minimal daily protein intake of 0.8 to 1.0 g/kgm to maintain nitrogen balance.

A positive nitrogen balance can improve HE by promoting hepatic regeneration and increasing the capacity of the muscle to detoxify ammonia.

The restriction depends on the degree of HE but severe malnutrition is associated with a poor short term prognosis as severe restriction can worsen liver function and increase the risk of death.

For these reasons, the current recommendation is to avoid severe restriction of dietary protein.

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Vegetables and dairy products cause less encephalopathy than does meat. Differences in a.a composition, the ratio of CHO to total protein and high content of non absorbable fiber could explain these effects.

BCAA correct the imbalance in the plasma a.a profile, nutritional status of patients with advanced cirrhosis and chronic HE who are intolerant of other protein sources.

inhibition of urease producing colonic bacteria

* **Non absorbable disaccharides:**

* lactulose is not broken down by intestinal disaccharidases and reaches the cecum, where it is metabolized by enteric bacteria to lactate and acetate and results in lowering of the colonic PH which creates an environment that is hostile to survival of urease producing intestinal bacteria and may promote the growth of non urease producing lactobacilli.

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- * The acidification of the colonic secretions not only reduces the absorption of ammonia but also result in movement of ammonia from the blood into the bowel lumen. It is also has a cathartic effect.
- * Lactulose is considered standard therapy for HE and durgs introduced for treatment of HE are invariably compared with it.
- * Oral lactitol is as effective as lactulose and has the advantage of being more palatable and associated with lower incidence of side effects such as flatulence.

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* **Antibiotics with activity against urease producing bacteria (Neomycin and metronidazole) :**

- * The efficacy of neomycin (4 g/daily) is similar to that of lactulose and the efficacy of metronidazole for one week (800mg daily) is similar to that of neomycin.
- * Rifaximin non absorbed derivative of rifamycin is approved alternative at a dose of 1200mg daily.

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- * Lactulose and neomycin may have an additive effect in reducing the intestinal production of ammonia accompanied by an enhanced clinical response in majority of patient who have an inadequate response to lactulose alone.
- * Inhibition of urease producing H.pylori remains unclear and the efficacy of eradication therapy has not been proved in controlled trials.

Increased metabolism of ammonia in the tissue (Fixation of ammonia)

- * **L-Ornithine and L-aspartate:** provides substrates for both ureagenesis and for synthesis of glutamine. Controlled trials suggest that both enteral and parental formulations of ornithine-aspartate significantly reduce ammonia levels and have useful therapeutic effects in patients with mild HE.

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* Zinc:

- * zinc deficiency is common in patients with cirrhosis and is caused by its loss in the urine.
- * Two of the five enzymes responsible for the metabolism of ammonia to urea are zinc dependent.
- * There are reports of overt HE precipitated by zinc deficiency and reversed by supplementation with oral zinc.
- * In controlled trial the rate of formation of urea from a.a and ammonia was increased in patients with cirrhosis, zinc deficiency and mild HE. Who were given 600 mg of oral zinc sulfate/day for 3 M.

Cont.

* **Sodium benzoate and sodium phenylbutrate**

Sodium benzoate combine with glycine to form hippuric acid the subsequent renal excretion of hippuric acid results in loss of ammonia ions. For each mol of benzoate the kidneys excrete 1 mole of nitrogen its effect was comparable to lactulose.

* sodium phenylbutrate is converted to phenylacetate which react with glutamine and subsequently excreted in the urine with loss of ammonia ions.

* **Levocarnitine:** was shown to be beneficial in lowering blood ammonia however, the result of clinical studies are conflicting.

Reduction of false neuro-transmitters

I.V or oral administration of formula rich in BCAA reduce the production of the false neurotransmitters. Although current result don't support the general use of BCAA as treatment of HE. They have specific role in improving nitrogen balance without precipitating HE in malnourished patients with cirrhosis who are intolerant of protein supplementation.

Inhibition of GABA benzodiazepine Receptors

Benzodiazepine receptor antagonist

(Flumazenil): controlled trials demonstrated incomplete improvement, it causes only transient improvement in the mental state. When there is response to flumazenil it occurs within few minutes after administration of the bolus.

Correction of manganese deposition in the basal ganglia

- * Clinical observations suggest that manganese may accumulate in the basal ganglia of patients with cirrhosis
- * Manganese deposition in the basal ganglia results in dopaminergic dysfunction.
- * Longitudinal studies are needed to investigate the possible therapeutic effects of chelation of manganese with edetate calcium disodium.

Dopaminergic drugs (levedepa and bromocriptine)

- * **Dopaminergic drugs** enhance dopaminergic neurotransmission to restore displacement of central neurotransmitters caused by false neuro-transmitters. When targeted to improve consciousness dopaminergic drugs did. Not yield satisfactory results, but improvement of extra pyramidal signs has been reported in patients with chronic HE.
- * **Opiate receptor agonists:** showed some benefit in ameliorating motor activity of rats with HE. But no studies have been done in humans.

Liver transplantation

Liver transplantation is indicated in patients with end stage cirrhosis many of whom have HE along with other manifestations of severe hepatic decompensation. Also, indicated in patients with severe, refractory HE, including dementia, spastic paraparesis, cerebellar degeneration and extrapyramidal disorders, even when HE is the sole manifestation of hepatic decompensation.

Management of the episode of acute HE

- * The diagnosis is supported by the presence of a time related precipitating factor and by a history of similar episodes. However, the neurologic manifestations can vary from the first to subsequent episodes. Exclude alternative diagnosis.
- * **supportive measures:**
 - * include the general care of a patient with changes in mental status. I.V. catheters, hydration, urinary and nasogastric tubes may be necessary. Avoid line sepsis, prevention of aspiration pneumonia prevention of pressure sores and adequate nutritional support.
 - * The current recommendation is to provide 25 to 35k cal. Kg.d and 0.5 to 1.2 g.kg d of protein or aa. During the initial period (2-3 days) the pt is treated with glucose supplements as I.V fluids. Then the oral diet can be reinitiated.

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* **Elimination of precipitating factors:** Multiple precipitating factors may be present systemic exclusion of all the precipitating factors is recommended. A common pitfall is not to exclude ongoing infection. It is wise to assume that a patient with HE has an infection until proven otherwise.

* **Administration of drugs:** Lactulose in large oral dose (30-50ml of lactulose every 1 -2 h) or as an enema (300 ml in 1–3 L of water). After catharsis begins the oral dose should be adjusted (15 – 30 ml four times a day) or lactulose enema every 6- 8 h. the dose of lactulose is titrated to produce 2 or 3 soft bowel movements daily.

Flumazenil: Its use to manage HE is not well standardized. It is available as I.V preparation that is administered as a bolus (0.4 – 2 mg). If a favorable response occurs additional dose can be given. Over dosage of flumazenil may have proconvulsant effects.

L-aspartate and L-ornithine.

Treatment of the patient with chronic HE

- * DD of chronic HE from other chronic degenerative disease of the CNS in patients with chronic liver failure.
- * Patients with chronic HE usually have severe malnutrition. The patient should have several small feedings (5 to 6/day) evening snacks are recommended with amount of protein in the diet should be individualized.

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- * Progressive increment on the total amount of protein should be tried. Tolerance to protein can be improved with feeding dairy products and vegetable based diets.
- * Oral BCAA are associated with a decreased number of acute exacerbations and with nutritional improvement.
- * Lactulose with dose adjustment to obtain 2 or 3 bowel movements/day. Care is needed to avoid excessive diarrhea and dehydration precipitated HE.
- * Neomycin or other antibiotics may be an alternative.

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- * Tests to monitor toxicity should be performed periodically, and periods of more than 6ms with the same antibiotics should be discouraged.
- * Management of problems associated with chronic liver dysfunction.
- * Ascites is better managed with paracentesis than with diuretic mild degree of edema is better than HE.
- * Variceal bleeding pharmacologic and endoscopic treatment are less likely to cause HE than TIPS or surgical shunting.

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* Liver transplantation in the care of patients with chronic encephalopathy, the decision to proceed to liver transplantation can be difficult. Severe chronic neuropsychological abnormalities usually are considered a contraindication to liver transplantation. However, Improvement of such manifestations have been reported after transplantation.

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- * Surgical exclusion of the colon should be reserved for the occasional patients with relatively good liver function and severe neurologic manifestations who are not candidates for liver transplantation. Colonic bypass is preferred because it is associated with a lower mortality than is colectomy.
- * A common subset of patients with chronic HE are those with post shunt encephalopathy due to surgical Portosystemic shunt or TIPS. Persistent and intractable encephalopathy may be managed by reduction of the stent diameter or occlusion of the shunt.

Management of HE in patients with fulminant hepatic failure

- * In patients with fulminant hepatic failure, therapy is directed at counteracting the multi organ failure as well as supporting the function of the impaired liver by extracorporeal liver assist devices like (MARS).
- * Any possible factor affecting mental state, such as hypoglycemia pharmacologic sedation and intracranial pressure must be excluded.

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- * Patients are treated in an ICU tracheal intubations is recommended at the onset of grade III encephalopathy. Intracranial hypertension secondary to brain oedema should be monitored by ICP transducers.
- * Early identification and management of mild increase in ICP delay the onset of severe episodes and allow time for a liver to become available for transplantation.
- * Sustained elevation of ICP and the development of pressure waves are managed with mannitol 0.5 to 1.0mg/kgm I.V over 30 minutes.
- * If renal failure develops, dialysis is needed. Blouses of indomethacin and mild hypothermia can be effective, glucocorticoids are not useful.

Management of minimal HE

- * There is some divergence of opinion as to whether treatment is warranted for patients with minimal encephalopathy.
- * Improvement of minimal HE after the same measures that are used to manage overt chronic HE was observed. Also the relation between minimal HE, ammonia level and the liver function was observed.
- * Intervention may enhance the capacity to perform practical tasks.

Summary and conclusion

- * Hepatic encephalopathy is a well recognized clinical complication of chronic liver disease. About 30% of patients with cirrhosis die in hepatic coma. Hepatic encephalopathy can occur in patients with fulminant liver disease without evidence of portal systemic shunting. These patients have increased intracranial pressure and brain edema with a deleterious clinical course and poor prognosis unless liver transplantation is available.

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- * The pathogenesis of portosystemic hepatic encephalopathy probably is multifactorial, although the predominant causative agent appears to be ammonia. Therapy includes timely recognition and correction of precipitating factors. Once the condition is manifested, standard therapy is acute administration of lactulose. The use of oral antibiotics and BCAAs is of some benefit in patients who do not respond to lactulose.

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- * Limitation of protein in the diet may be useful for short periods but is not recommended for long-term use because of potential worsening of already poor nutrition.
- * Several experimental therapies based on potential pathogenetic mechanisms have not resulted in improved outcomes over standard therapy with lactulose. However future research will likely focus on the correction of alterations in neurotransmission. It is hoped that newer therapies will provide protection from putative neurotoxins that cause secondary defects in neurotransmission.

A white rectangular card is the central focus, featuring the words "Thank you" in a bold, red, sans-serif font. The card is set against a dark blue background. To the left, there are delicate white baby's breath flowers. To the right and top, there are large, vibrant yellow lilies. A red ribbon is draped across the bottom of the card, adding a decorative touch.

Thank you