Fulminant hepatic failure

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Abstract

Fulminant hepatic failure is a devastating disease occurring as a complication of various forms of liver diseases in both children and adults. The objectives of this article is to update the knowledge of physicians, on the most important and recent advances related to this condition with the ultimate goal of improving patient care.

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Fulminant hepatic failure (FHF) is a rare complication of liver disease. FHF is defined as acute liver failure complicated by hepatic coma occurring within two weeks of jaundice. A subfulminant or late onset hepatic failure (SFHF) occurs from two weeks to three months from the onset of clinical jaundice. The distinction between these two forms has etiologic and prognostic implication [1],[2] .

Etiology

Viral hepatitis is the commonest cause; accounting for 60-75% of all cases. All viral infections causing acute hepatitis may be complicated by FHF. However, FHF occurs in about 0.1 % of all acute HAV infections and is associated with better survival (40%). FHF following HBV and HDV infections occurs more frequently and has a

poorer survival rate (10-20%). FHF occurring in HBS Ag positive patients is not always due to HBV infection. In a world-wide survey of 377 cases of FHF in persons positive for HBsAg, only 52% could be attributed to infection with HBV, 30% were caused by HDV coinfection or superimposed on HbsAg carriers, and the cause of hepatitis could not be identified in 18% [3] . FHF is also common following HCV, but it is less common complication of HEV infection. Drug-induced hepatitis is the second major cause accounting for about 20% of the causes of FHF. The number if hepatotoxic drugs is very large and most of them have been associated with FHF. Although the clinical course is usually subfulminant, the survival rate is very low (<5%), except for acetaminophen- and isonizide-induced cases. Miscellaneous causes include, other infections such as tuberculosis and leptospirosis, sickle cell disease (hepatic sickling) metabolic liver diseases (Wilson's disease, Alpha-l-antitrypsin deficiency), toxins such as Amanita mushrooms, and aflatoxins; and vascular causes such as Budd-Chiari syndrome More Details.

In neonates, galactosemia, hereditary fructose intolerance, tyrosinemia, and idiopathic neonatal hepatitis may present as FHF.

Pathogenesis

The Pathogenesis of liver disease is uncertain. It is still not known why only few patients develop FHF following liver insults. Direct cytotoxic effects and/or hyperimmune response to antigen, coinfection with two or more viruses may be the initial events that, for still unknown reason, trigger rapid progress to liver failure instead of the usual recovery [4],[5] . The *pathogenesis of hepatic encephalopathy (HE) is also controversial*, but most probably multifactorial. Ammonia intoxication is common in patients with hepatic coma. Ammonia is produced by degradation of proteins and gluconeogenesis from aminoacids by colonic bacteria. However, serum ammonia levels are not increased in all patients with HE, and high levels may be present without coma. Nevertheless, if serum ammonia levels are increased, there is frequently a correlation between levels and degree of HE. In addition, ingestion of nitrogen-containing substances worsens the encephalopathy, whereas therapeutic interventions that decrease ammonia levels (e.g. antibiotics and lactulose) are associated with improvement in encephalopathy. False neurotransmitters (Fts) include gamma-amino butyric acid (GABA), octopamine, serotonin, catecholamines, phenylethanolamines and others. GABA, octopamines and phenylethanolamines are produced by intestinal flora. GABA is the main inhibiting neurotransmitter in mammals and serum levels are very high in hepatic coma especially after hemorrhage. The other Fts are also elevated. These substances interfere with neurotransmission and are implicatd in the reversible deficits seen in this disease. Serum levels of short chain fatty acids (butyrate, valerate, octonoate) are high in hepatic coma but unlike GABA there is no correlation between their levels and degree of coma [6] . The amino acids profile in hepatic coma is abnormal. Serum phenylalanine, tyrosine, tryptophan and methionine are increased, while branched-chain amino acids (valine, leucine, isoleucine) are decreased. However, branched-chain amino acid therapy is probably not more effective than nonselective amino acid administration. Other metabolic abnormalities have been found in hepatic coma but their significance remains unclear. The *Pathogenesis of cerebral edema in FHF remains uncertain.* However, vasogenic

and cytotoxic mechanisms have been suggested. In the former, the break down of the blood-brain barrier, allows serum proteins to leak through the normally selectively permeable capillary endothelium. This leads to the accumulation of these fluids in the brain parenchyma. In cytotoxin-induced edema there is accumulation of hypotonic fluids within the brain. However, these two processes may coexist in the same patient [7] . Regardless of the cause, increased intracranial pressure (ICP) plays an important role in the genesis of cerebral edema. Cerebral perfusion pressure (mean arterial pressure - intracranial pressure) is a useful prognostic indicator. Unlike many other conditions associated with increased ICP, cerebral blood flow is usually normal in FHF, indicating a poor correlation between these two factors [8],[9],[10] .

Clinical Features

All symptoms and signs develop during the course of ordinary hepatitis that instead of improving progress to deterioration with increased jaundice, encephalopathy, bleeding, edema, and ascites, and possibly acute renal failure [11],[12],[13] . Cerebral edema occurs in 40-85% of the patients with FHF of late stage III and IV, but is less frequent in SFHF [14] . Cerebral edema is more common in patients with HB V and HCV than in those with HAV infection, and it is the leading cause of death in these patietns [15] . Typical indicators of increased ICP such as headaches and papilledema are usually absent, but systolic hypertension and increased muscle tone that progressess to decerebrate posturing constitute the earliest signs and occur when the ICP exceeds 30 mm Hg [16] . This may lead to cerebral herniation and respiratory arrest unless treatment s started early. Cerebral edema, intracranial hemorrhage, hypoglycemia, hypotension, sepsis, and portosystemic encephalopathy, may all produce rapid decompensation and require urgent diagnostic and therapeutic measures. Reduced liver span is an ominous sign. Deterioration of mental status and level of consciousness occur over several hours or days, depending on the degree of evolution of hepatic necrosis. The stages of hepatic encephalopathy are: Stage I - delayed response with or without asterixis, altered sleep habits. Stage II - drowniness but responsive to simple commands. Stage III - stuporous but responsive to painful stimuli. Stage IV - comatosed unresponsive to painful stimuli. Hyperpnea and hypothermia may be present. Clonus and hyperreflexia seen early are replaced by loss of deep tendon reflexes, corneal and pupillary reflexes. Staging of the HE is important for following the progression of the disease, therapy and prognosis. Because the above staging applies mostly to adults, a modified Glasgow coma scale has been suggested for infants and young children [17] . This pediatric coma scale [Table - 1], assumes that in the first six months of age, the best verbal response is a cry (2 points); between 6 and 12 months, the best response would be a noise (3 points), and words would be the best verbal responses after 12 months of age (4 points). On the other hand, the best motor response in the first six months of age is flexion (3 points), and between 6 and 12 months, the best motor response is pain localization (4 points). Accordingly, normal scores are age-related as follow: 0-6 months = 9; >6-12 months = 11;>12-24 months = 12;>24-60 months = 13;>5 years = 14 (best adult score).

Laboratory Data

Rising bilirubin and aminotransferases that normalize rapidly, then become very low in a patient who is still clinically unstable are strongly suggestive of FHF and reflect changes in hepatic function. Similarly, alkaline phosphatase and related enzymes levels are useful standards to evaluate intrahepatic biliary tract obstruction. Assessment of the patient's coagulation status is another important measure of hepatic reserve. Factors II (Fibrinogen), V, VII, IX and X are synthesized by the liver, and all except V are vitamin K dependent. Therefore, prothrombin time and factor V have prognostic significance and thus should be monitored. Serum ammonia level is usually elevated and EEG is mostly indicated to evaluate progression to brain death. The cause of FHF may be identified by the use of appropriate viral serology, and relevant laboratory investigations.

Pathology

Fulminant hepatitis results in massive necrosis of the hepatocytes which progresses rapidly. There is destruction of the limiting plates and disorganization of the architecture of the liver. Necrosis may be patchy or confluent resulting in collapse of the reticulin frame work; or may be centrilobular (acetaminophen toxicity, shock). Residual or regenerating nodules of hepatocytes are rarely seen. These changes are important to understand the disease, but liver biopsy is usually not required for the diagnosis and management of this condition.

Management

1. Medical therapy

The aim of medical therapy is to prevent or correct metabolic abnormalities until hepatic regeneration occurs or until a liver donor is found for transplantation. Patients require intensive care monitoring and supportive care in the form of parenteral hydration with attention to electrolytes, prevention or correction of hypoglycemia, nutritional support with protein restriction aiming at the reduction of urea synthesis; whereas neomycin and lactulose are aimed to reduce the colonic production and absorption of ammonia. The effects of branched-chain amino acids infusion is controversial [18],[19] . Prostacyclin (PGI2), a wellknown vasodilator, may improve tissue hypoxia.

Steroids and prostaglandin E infusion are generally of no value [20],[21],[22],[23],[24] . *Coagulation abnormalities* may be corrected with parenteral Vitamin K. In cases of no response to vitamin K, or suspicion of disseminated intravascular coagulopathy, fresh frozen plasma is indicated with or without platelet concentrate infusion. Plasma exchange has been suggested as another means that may correct homeostasis [25] . The reduction of gastric acidity by early use of H2-antagonists is important to pevent stress-induced gastroduodenal disease and subsequent hemorrhage. *Cerebral edema* is

a major complication of increased ICP and a common cause of death. Early detection is the key for effective treatment. Patients at risk of increased ICP should be placed in a head-up position with elevation of the trunk about 20° above the horizontal [26] . However, higher elevation (≥ 40°) possibly produce paradoxical elevation of the ICP [27] .Monitoring of the ICP by extradural transducers allows not only early detection of increased ICP but also guidance of therapy to prevent brainstem herniation [28],[29] . Although the overall survival rate is not significantly improved in monitored patients, survival from the onset of grade 4 to death was significantly longer in monitored patients. This has considerable implications for transplantation. However, ICP monitoring does haveserious complications such as infection and intracranial bleeding [30] . Mannitol boluses reduce ICP and more importantly increase the overall survival rate. However, because of the nephrotoxicity of this drug, urine output and serum osmolarity need to be monitored and, in patients with renal failure, mannitol should be used only in conjunction with hemofiltration or ultrafiltration [22] . Hyperventilation , although effective on short term basis, seems to have no effect on the frequency nor on the severity of cerebral edema [31] . Dexamethasone , as indicated earlier, has not been shown to be effective in the treatment of cerebral edema inpatients with FHF. Barbiturates especially thiopental (3-5 mg/kg) is given by slow intravenous infusion every 15 minutes until signs of increased ICP disappear (Mx 500 mg). This modality controls the ICP in the majority of patients and, therefore, is indicated especially when mannitol fails [32] . The development of *acute renal failure* should be suspected when creatinine level is rising despite low to normal BUN (liver unable to convert ammonia to BUN) and treated with hemodialysis. However, continuous hemofiltration with or without hemodiafiltration is preferred by some authors. Other measures such as exchange transfusion, plasma exchange, hemoperfusions via animal livers or charcoal have similar objectives of removing toxins but do not improve outcome. Respiratory and cardiovascular support is provided as indicated and antibiotics are frequently administered to combat infection. Acetylcysteine has been suggested in postparacetamol FHF. This drug is highly effective and safe even when it is given later than 10 hours after the overdose [33] . Artificial liver support devices are designed not only to remove circulating toxins but also to perform complex metabolic functions [34],[35] . In these Extracorporeal Liver Assist Devices (ELAD) the blood of the patient is perfused through fiber cartridge containing living hepatocyts. Although preliminary data are encouraging, further studies are needed [36] . Hepatic regeneration by growth factors stimulating hepatocyte proliferation, especially insulin and glucagon was reported to be successful. However, a randomized study found no effects [37] . A scheme of various therapeutic measures is depicted in [Table - 2].

2. Orthotopic Liver Transplantation (OLT)

Despite all these medical measures, the mortality rate remains very high varying from 50-85%. This has led to the introduction of OLT which reversed the prognosis with survival rates from 60-80% [38],[39] . Guidelines to select patients who are unlikely to survive without OLT have been suggested [40],[41] . These criteria include: Prothrombin time > 100 seconds or any three of the following: 1) Age <10 or > 40 years. 2) Non-A, Non-B hepatitis, halothane or other drugrelated etiology. 3) Duration of jaundice before onset of encephalopathy > 2 days.4) Prothrombin time > 50 seconds. 5) Serum bilirubin > 20 mg/dl. In Paracetamol - induced FHF: 1) pH> 7.3 or 2) Prothrombin time > 100 seconds and 3) Creatinine > 2 mg/dl. 4) Grade III or IV encephalopathy. Other Criteria included factor V < 20% or < 30% in patients below 30 years of age

with confusion or coma. These criteria although still widely used were found to be poor when tested in other centers [42] . Accordingly, it has been suggested that every patient with FHF should be evaluated for OLT. If the need for transplantation becomes clear or persists, the operation should proceed. If the OLT is no longer needed or contraindications emerge at the time a donor is available, the organ can be used for another patient.

Prognosis

The majority of patients recovering from FHF do so completely, with only a small number of cases who will have neurological sequelae most probably as a consequence of brain edema [43] . Prognosis depends on the depth of coma at presentation, factor V level, and alpha fetoprotein level. Mortality is highest for patients presenting in stage IV and for those who have very low factor V level; whereas increasing alpha fetoprotein level is associated with better prognosis.

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Table 1: Glasgow Coma Scale

	Adult	Pediatric
EYES OPEN		
• Spontaneous	4	same
• To speech	3	same
• To pain	2	same
• None	1	same
BEST VEBAL RESPONSES		
- Oriented	5	Oriented5
- Confused	4	Word 4
- Inappropriate	3	Vocal sounds 3
- Incomprehensible	2	Cries 2
- None	1	None 1
BEST MOTOR RESPONSES		
• Obeys commands	5	same
• Localizes pain	4	same
• Flexion to pain	3	same
• Extension to pain	2	same
• None	1	same

* for score interpretation, see text.

Table 2: Therapeutic Guidelines

1. Nutrition - Sufficient calories (oral, NG,or IV)
   - No need to Ø proteins (usually)
   - branched-chain amino acids

2. Prevent hypoglycemia (oral glucose or D10 IV).
3. Monitor electrolytes: Hypokalemia.
4. Monitor acid-base balance: Correct abnormalities.
5. Monitor renal functions, oxygenation, ventilation.
6. Reduce production of ammonia/toxins.

- Diet + branched-chain aa,lothers.
- Neomycin oral 25 mg/kg Q 8H.
- Lactulose 50% syrup:

• Oral 1 ml/kg Q2-4H . - diarrhea, then |.
•Enema: dilute syrup in water 1:3 give 100-300 ml twice to thrice daily.

7. Reduce gastric acidity: H2 antagonists.
8. Antibacterial and antifungal prophylaxis ?
9. Correct coagulation disorders.
10. Liver support: ? Toxin removal

- Peritoneal/hemodialysis-exchange transfusion.
- Plasmapheresis, hemoperfusion, hemofiltration.
- Artificial liver support device.

11. Cerebral edema:

- Monitoring - Positioning
- Mannitol - Thiopental
- Hyperventilation

12. Consider orthotopic liver transplantation.