Fulminant hepatic failure : is it a preventable syndrome ?

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Fulminant hepatic failure (FHF) is a complex syndrome due to the major deterioration of vital liver functions. It is characterized by the occurrence, during the course of an acute liver disease, of a metabolic encephalopathy always preceded by the decrease below 50 per cent of normal in coagulation factors activity (1). The cause may be acute hepatitis (due to hepatotropic viruses, hepatotoxic drugs, or poisoning such as acetaminophen overdose), acute hepatic hypoxia, acute exacerbation of chronic liver disease (auto-immune hepatitis, Wilson's disease), microvesicular steatosis (drugs, Reye's syndrome or acute fatty liver of pregnancy), exceedingly extended partial hepatectomy in patients with chronic liver disease or, in exceptional cases, life-saving total hepatectomy (1). The survival rate after FHF is heterogeneous, ranging from 50% (in young patients with acetaminophen-induced poisoning or hepatitis A) to 10% or less (in patients older than 40 and in those affected by some drug-induced hepatitis) (1). Although parameters with significant prognostic value were found in several studies using multivariate analysis methodology (2-4), adequate individual prognosis is often difficult to establish especially in patients with high grade of coma (1). Finally, emergency total liver transplantation (LT) increased the total 5-year survival rate, but implies major inconvenience including a 10-30% overtransplantation rate (5) and life-long immunosuppression in survivors. Thus, because of its high influence on the patient's prognosis and quality of life, prevention of FHF (6) must be a major concern in patients at risk of, or with already established, acute liver disease.

Prevention of the cause

Prevention of the cause is the most cost-saving measure against FHF.

Prevention of viral hepatitis

Vaccination against hepatitits B virus (HBV) is cost effective for preventing new cases of infection with HBV (and hepatitis D virus) and, thus, fulminant hepatitis B or B+D (7). Although recommended, universal vaccination against HBV is not yet achieved, even in the West. Currently, main target subjects include newborns or very young children, especially when one of the parents is being (or at high risk to be) chronic HBV carrier (in such cases, sero-vaccination is indicated at birth) and non immunized people (including physicians and other health-care workers) at high risk to be in contact with persons at high risk to be HBV chronic carriers. The worldwide spread of this vaccination still requires a decreased cost, but also continual education of the medical community. Acupuncture needles must be used only once to obviate silent, iatrogenic transmission of HBV infection. Vaccination against hepatitis A virus (HAV) is recommended in all non immunized individuals at high risk to become infected (7). A combined vaccine against HAV and HBV is now available.

Prevention of drug-induced acute hepatitis

This prevention requires a continuous, and increased, educational information of patients as well as physicians. The key rule for best preventing severe drug-induced side-effects is to stop using any drug early when new symptoms develop. Hepatotoxicity of therapeutic doses of acetaminophen may occur during a febrile, infectious disease (listeriosis, malaria, dengue) (personal experience) and is increased in patients fasting or not feeding regularly (including young children), in those given isoniazid or anticonvulsants, and in those given acetaminophen chronically with a low feeding behavior.

Prevention of other causes

Extreme cautiousness, including the advice of a pharmacist, before eating wild mushrooms will help to prevent mushroom poisoning. Prevention of heat stroke and that of recurrent cardiac arrhythmias will prevent cases of fulminant hypoxic hepatitis. Prevention of post-operative FHF is based on the limitation of excessive extension of hepatic resection, especially in patients with preoperative liver dysfunction.

Prevention of the fulminant and subfulminant course of established acute liver diseases

In patients with acute liver disease and a 50%, or more, decrease in coagulation factor activity — a mandatory step before clinical encephalopathy — an immediate (even nocturnal) advice by an hepatologist is warmly recommended. Immediate admission to a liver unit is especially suitable in patients with overt or deep jaundice, and in those older than 40, for preserving prognosis (admission before encephalopathy has a favourable influence), the efficacy of the etiologic liver treatment (8) and, when LT is required, the opportunity to perform auxiliary LT (9).

Drug(s) (or herbal medicines) could be either the cause of acute hepatitis or (mainly sedative, hepatotoxic and nephrotoxic drugs) an aggravating factor of an otherwise common acute viral hepatitis. In any patient with possible symptoms of acute liver disease, their administration must be stopped immediately, except insulin in insulin-dependent diabetic patients (lowered doses) and quinine in those suffering, or at risk of, falciparum malaria. Full restriction in potentially nephrotoxic drugs is crucial for preventing superimposed drug-induced renal failure, a factor of aggravated prognosis when encephalopathy develops. In all the risky situations of acetaminophen hepatotoxicity, including any acetaminophen overdose, early IV administration of N-acetylcysteine, a non toxic glutathion precursor, at least will prevent severe liver damage.

In pregnant women in the 3rd trimester, polydipsia, nausea or vomiting must lead to early diagnosis of acute fatty liver of pregnancy and early cessation of pregnancy, thus allowing a 100% maternal and fetal survival rate. In young patients with the acute form of Wilson's disease (acute liver disease, hemolytic anemia and moderate increase in serum transaminase activity), early administration of high doses of D-penicillamine must be started on clinical grounds. In patients with hypoxic hepatitis, urgent determination and prevention of early recurrence of the cause of the transient reduction in cardiac output should avoid further aggravation of the liver lesions. Prevention of severe forms of herpes simplex hepatitis requires early clinical diagnosis (recent treatment with immunosuppressors, persistent high fever $> 38°C$, serum aminotransferase activity above 50 times normal), blood and (if possible) liver sampling for virological studies and, finally, early administration of IV acyclovir. In patients with severe acute hepatitis due to HBV reactivation, whether antiviral therapy significantly prevents the occurrence of FHF is still unknown.

Prevention of further aggravation in patients with fulminant hepatic failure at the onset

When clinical encephalopathy is just beginning, all previous measures (including IV N-acetylcysteine) must be applied (even in the middle of the night). Rapid transfer to a liver unit is mandatory, sometimes by helicopter or even by plane. Early intubation is required in comatose patients. We still recommend to do all one can not to use drugs in order not to alter the natural history of the syndrome. In restlesness patients, patient's restraint may be needed.

Conclusion

At least in its most severe forms, FHF undoubtedly is a preventable syndrome. Main preventive measures include a more extended use of vaccines against HBV and HAV, the early cessation of drugs when new symptoms appear during their use, and admission to a liver unit (or at least early, even nocturnal, hepatologic advice) when prothrombin ratio is lower than 50% during the course of an acute liver disease.

References

1. BERNUAU J., BENHAMOU J.P. Fulminant and subfulminant hepatic failure. *In*: BIRCHER J., BENHAMOU J.P., MCINTYRE N., RIZETTO M., RODÉS J. Oxford Textbook in Hepatology. Oxford University Press, Oxford, 1998 (2nd edition, in press).
2. BERNUAU J., GOUDEAU A., POYNARD T. *et al.* Multivariate analysis of prognostic factors in fulminant hepatitis B. *Hepatology*, 1986, **6** : 648-651.
3. O'GRADY J.G., ALEXANDER G.J.M., HAYLLAR K.M., WILLIAMS R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology*, 1989, **97** : 439-445.
4. ACHARYA S.K., DASARATHY S., KUMER T.L. *et al.* Fulminant hepatitis in a tropical population : clinical course, cause, and early predictors of outcome. *Hepatology*, 1996, **23** : 1448-1455.
5. HOOFNAGLE J.H., CARITHERS R.L., SHAPIRO C., ASCHER N. Fulminant hepatic failure : summary of a workshop. *Hepatology*, 1995, **21** : 240-252.
6. BERNUAU J., DURAND F. L'insuffisance hépatique fulminante et subfulmiunante, urgence de prévention. *Gastroenterol Clin Biol*, 1997, **21** : 387-390.
7. LEMON S.M., THOMAS D.L. Vaccines to prevent viral hepatitis. *N Engl J Med*, 1997, **336** : 196-204.
8. BERNUAU J. Liver treatments in acute liver failure (including antidotes, antiviral therapy and enhancement of regeneration). *In*: ARROYO V., BOSCH J., BRUGUERA M., RODÉS J. Therapy in liver diseases. The pathophysiological basis of therapy. Masson, Barcelona, 1997, pp. 357-364.
9. CHENARD-NEU M.P., BOUDJEMA K., BERNUAU J. *et al.* Auxiliary liver transplantation : regeneration of the native liver and outcome in 30 patients with fulminant hepatic failure. A multicenter European study. *Hepatology*, 1996, **23** : 1119-1127.