Eur J Med Res (2008) 13: 87-91

COURSE AND THERAPY OF ACUTE LIVER FAILURE

L. Leifeld[1], Ph. Merk[1], V. Schmitz[1], J. Nattermann[1], J. C. Kalff[2], A. Hirner[2], T. Sauerbruch[1], U. Spengler[1]

[1]Department of Internal Medicine I, [2]Department of Surgery, University of Bonn, Germany

Abstract

Objectives and Methods: Despite liver transplantation and advances in intensive care medicine fulminant hepatic failure [FHF] remains a life-threatening condition. Actual observations of the clinical course of these patients are rare. Therefore, we analyzed course of disease and survival in all patients treated for FHF at the University of Bonn between 1998 and 2004 and compared it to the patients treated for FHF during 1992-1997.

Results: 35 patients were treated for FHF during this period. FHF was viral induced in 13 patients (HBV n = 11, HAV n = 2), toxic in nine, cryptogenic in eleven and autoimmune and hyperthermia in one patient each. According to London- and/or Clichy criteria 16 patients were transplanted. Four of them died during the first year after transplantation due to infectious and hemorrhagic complications. Three patients died without liver-transplantation. All together, 1-year survival was 80%.

When compared to patients with FHF analyzed in the period 1992-1997 numbers of patients with FHF in our centre had increased from 16 to 35 patients and 1-year survival improved from 67.5% to 80%. This improved survival was associated with a lower proportion of transplanted patients (45% versus 68%).

Conclusions: These changes reflect advances in therapy of patients with FHF, which enables a greater proportion of patients to survive without the need for transplantation.

INTRODUCTION

Fulminant hepatic failure [FHF] is a rare but still life-threatening disease. The disease is characterized 1) by acute liver cell damage leading to jaundice and coagulopathy, 2) by the appearance of hepatic encephalopathy and 3) by the absence of a previous liver disease. Based on the time between jaundice and hepatic encephalopathy FHF can be classified as hyperacute liver failure (<7days), acute (1-4weaks) and subacute form (5-12 weeks) [1] Other authors defined FHF as a liver failure within 7 weeks after the first onset of signs of liver damage [2], or restricted the term FHF to patients who develop encephalopathy within two weeks and the term "subfulminant hepatic failure" to those who develop encephalopathy in 2 to 12 weeks after jaundice [3]. Those patients with the most rapid onset of encephalopathy have the best chance of spontaneous recovery compared to those with subacute liver failure [1].

Indication for high urgent liver transplantation is critical. On the one hand death may occur in those patients who are not transplanted in the hope for spontaneous recovery. On the other hand the outcome of liver transplantation in FHF may be worse than the putative spontaneous course especially since results of transplantation in FHF is somewhat less optimal than in elective transplantation. Therefore, prognostic scores have been developed to assist the decision, whether to transplant or not to transplant.

The Kings-College liver transplant unit ("London criteria") differentiates between paracetamol versus non-paracetamol-related hepatic failure based on distinct laboratory values (pH, creatinine, prothrombin time, bilirubin) and clinical data (age, etiology, duration) [4]. Alternatively, Clichy criteria include encephalopathy and factor V as prognostic markers indicating the urgent need for liver transplantation [5].

Recently, we analyzed the follow up of patients with FHF treated at the University of Bonn between July 1992 and July 1997 [6]. In that study of 16 patients 60 day survival was 75% and one year survival was 68%. Nearly 70% of the patients were transplanted. Now, we supplement this data by an analysis of all 35 patients with FHF treated in the subsequent years (January 1998 to December 2004) to identify changes in the management and outcome.

METHODS

We analyzed the follow-up of all patients, who had been treated for FHF or acute hepatitis at the University of Bonn between January 1998 and December 2004. FHF was defined by the presence of severe acute liver disease with jaundice and coagulopathy accompanied by a hepatic encephalopathy in a previously healthy person [10]. Time between jaundice and hepatic encephalopathy had to be shorter than 8 weeks. For comparison, we included patients with acute hepatitis into our analysis. These patients had also severe acute hepatitis and imminent FHF but did not fulfill the criteria for FHF.

Extensive charts were analyzed for gender, age, etiology, concomitant diseases, body mass index, blood pressure, prothrombin time (minimal, at hospitalization, at death or discharge), factor V (minimal, at hospitalization, at death or discharge), factor X (minimal,

Table 1.

		acute liver failure				Acute hepatitis
	Total	**Survived without transplantation**	**Deceased without transplantation**	**survived with transplantation**	**deceased with transplantation**	**Total**
Number of patients	35	16	3	12	4	56
Gender (male/female)	12/23	6/10	_	3/9	2/2	39/17
Age	40 ± 14	39 ± 1	47 ± 14	41 ± 7	32 ± 13	34 ± 13
Body mass index	22 ± 4	22 ± 4	17 ± 9	23 ± 8	24 ± 6	24 ± 4.6
Quick (minimal) (%)	17 ± 11	25.6 ± 11	6 ± 1	11 ± 3.7	12 ± 3	62 ± 28
Factor V (minimal) (%)	24 ± 16	32.6 ± 20	6.6 ± 3	18.7 ± 5	18.5 ± 5	82 ± 46
Factor X (minimal) (%)	24 ± 14	28.4 ± 16.7	21 ± 17.6	18.8 ± 8	23 ± 7	45 ± 30
Antithrombin III (minimal) (%)	23 ± 13	30.7 ± 15.4	14.6 ± 12.6	19 ± 11	23 ± 13	59 ± 30
Bilirubin (maximal) (mg/dl)	15 ± 10	10.5 ± 9.7	12.6 ± 12	13.6 ± 7	25.5 ± 7	13 ± 11
ALT (maximal) (U/l)	2311 ± 2310	3048 ± 2844	3761 ± 2691	1351 ± 978	764 ± 469	1562 ± 1515
Creatinine (maximal) (mg/dl)	2,0 ± 2,2	1.7 ± 1.9	5.1 ± 4.6	1.5 ± 1.6	2 ± 1.9	1,1 ± 0,6
Hepatic encephalopathy (maximal)	2.4 ± 1	1.8 ± 0.94	3.3 ± 0.76	2.9 ± 0.78	2.5 ± 0.58	0 ± 0

Table 2.

	Numbers (male: female)	**Indication for LTX (Clichy or London)**	**Death on waiting list or contra-indications for transplantation**	**Improvement despite former indication for LTX**	**LTX performed**	**1 year survival after LTX**	**1 year survival total**
HBV	11 (5:6)	8	1	1	6	6/6 (100%)	10/11 (91%)
HAV	2 (1:1)	1	0	1	0	0	2/2 (100%)
Toxic (*)	9 (2:8)	4	1	1	2	1/2 (50%)	7/9 (78%)
Other (**)	2 (1:1)	1	0	9	1	1/1 (100%)	2/2 (100%)
Cryptogenic	11 (3:7)	9	1	1	7	4/7 (57%)	7/11 (64%)
Total	35 (12:23)	23	3	4	16	12/16 (75%)	28/35 (80%)

(*) paracetamol n = 3 – in one patient in combination with diphenhydramine - and amanita poisoning, ecstasy, halothane, isofluran, thiamazol and isoniazid in one patient each
(**) hyperthermia n = 1 and fulminant autoimmune hepatitis n = 1

at hospitalization, at death or discharge), AT III (minimal, at hospitalization, at death or discharge), bilirubin (maximal, at hospitalization, at death or discharge), creatinine (maximal, at hospitalization, at death or discharge), pH (minimal), grade of hepatic encephalopathy, HIV-serology, fulfillment of London- and Clichy criteria, duration of hospitalization at the University of Bonn and at referring hospitals, duration of intensive care treatment, necessity and duration of mechanical ventilation, necessity and duration of renal dialysis, necessity and duration of treatment with vasopressors, necessity to substitute coagulation factors, treatment with lamivudine in hepatitis B, and survival.

All statistical calculations were performed with SPSS software package. Data are given as mean ± standard deviation. Correlations between groups were analyzed by Pearson correlation index. Differences between the groups were compared by the non-parametric Mann-Whitney-U test.

RESULTS

Between January 1998 until December 2004 35 patients with FHF were treated at the University of Bonn. Most FHF were virally induced (37%), by an acute hepatitis B in 11 patients, and hepatitis A in 2 patients. 9 patients (26%) had toxic etiologies. In nearly a third (31%) of the patients the etiology remained unclear despite extensive diagnostic work up. Clinical data, selected laboratory values and clinical outcome with respect to the etiologies are summarized in Table 1 and 2.

In 23 of the 35 patients with FHF, London and/or Clichy criteria for urgent transplantation were fulfilled (Table 2).

Among these 23 patients 3 had contraindications for transplantation and/or died while waiting for a donor organ; one with amanita intoxication with advanced bowel necrosis, one patient with cryptogenic FHF refused transplantation and a further patient with hyperacute hepatitis B died from multi-organ failure one day after being listed for transplantation waiting for an organ. Four patients of the 23 patients who fulfilled London or Clichy criteria improved their condition without liver transplantation.

16 of the 23 patients were transplanted (Table 2). Two of the 16 transplanted patients died within the first two months after transplantation (2-month survival 88%), two further patients died within the first year (1-year survival 80%)(Table 2). Death of transplanted patients occurred due to infectious complications in three of these four patients (septicemia caused by aspergillus infection, respiratory failure following pneumonia and chologenic liver abscess and septic multi-organ failure in the third patient). The fourth patient died from a severe haematothorax after puncture of his subclavian vein with subsequent hypoxic brain damage. One patient had to be retransplanted after two years because of chronic rejection. At this time the kidney was also transplanted because of renal failure.

Altogether, survival of transplanted patients with FHF was 86% after two months and 80% after one year.

Intensive therapies were necessary to reach this outcome. In-patient treatment time was 37 ± 32 days, whereby 80% of the patients required intensive-medical support for 15 ± 17 days. Intensive care included artificial respiration in 63% of the patients and extracorporal dialysis in 31%. 37% of the patients required vasopressor therapy and 71% substitution of coagulation factors. Among the 11 patients with fulminant hepatitis B 7 patients received lamivudine. None of them died but 3 had to be transplanted. 91% of the patients had been treated in other hospitals before referral (on average for 5 ± 4 days). Interestingly, worse outcome correlated with delayed referral to our tertiary unit (correlation to death: $r = 0.39$ $p = 0.019$; correlation to need for transplantation $r = 0.38$ $p = 0.024$). Referral to our centre occurred 16 ± 21 days after onset of the disease for patients who were transplanted, 4 ± 3 days for the patients who were not transplanted, 21 ± 29 days for deceased patients and 6 ± 6 days for the patients who survived.

Death was also correlated to the minimum Quick value and fulfillment of London or Clichy criteria ($p<0.05$). When analyzing all patients with a severe course including both, death and need for liver transplantation, we found correlations to London or Clichy criteria, Quick value, bilirubin, grade of hepatic encephalopathy, necessity for intensive care medicine, mechanical ventilation, renal dialysis, vasopressors or coagulation factors and the duration until referral to our centre.

Outcome in these patients with FHF contrasted to 56 patients with severe hepatitis who were referred in the same period but did not fulfill the criteria of FHF. 42 (75%) of them had a viral hepatitis (HBV n = 24, HAV n = 8, HCV n = 5, HBV+HDV n = 4, HAV+HBV n = 1), 10 (18%) had a toxic hepatitis (paracetamol n = 5, amanita phalloides n = 1, ecstasy n = 1, dihydralazin n = 1, carbamazepine n = 1, phenprocoumon n = 1), one suffered from an autoimmune hepatitis and three had a cryptogenic hepatitis. Laboratory parameters of these patients are summarized in Table 1. A single patient died from a bleeding gastric ulcer one month after the onset of acute hepatitis B. This patient had marked coagulopathy (factor V 49%). All other patients with acute hepatitis survived throughout the whole observation period. Treatment lasted 9 ± 9 days with 6 ± 7 days in primary care hospitals. To prevent imminent hepatic failure 8 of the 24 patients with severe acute hepatitis B received lamivudine. None of them developed FHF. No prognostic marker was found to discriminate patients developing hepatic encephalopathy and FHF.

DISCUSSION

One year survival in our patients with FHF was 80% in the 1998-2004 period, indicating a substantial improvement as compared to our previous analysis of patients with FHF which indicated a one-year survival of 67.5% in the 1992-1997 period [6]. In our study 16 of 35 patients (45.7%) with FHF were treated by liver transplantation, a lower fraction than in the 1992-1997 period when 68% of the patients had to be transplanted. Now, two-month survival after liver transplantation was 87.5% and one year survival was 80%. These survival rates after liver transplantation demonstrate that transplant centers with an intermediate size can reach excellent results compared to other centers [4, 7-15]. Furthermore, we observed a marked increase in the numbers of patients treated for FHF (35 patients in the 1998-2004 period versus 16 patients in the 1992-1997 period). Interestingly, survival correlated with a short period between first symptoms and referral to our centre underlining the advantages of a more specialized early diagnostic and therapeutic management in more specialized centers.

This positive development in survival can be explained by an improvement of different factors in the management of patients with FHF:

Of note early application of lamivudine in patients with imminent severe hepatitis B might be an important step to improve survival in these patients. Hepatitis B is the largest subgroup of patients with FHF. Therefore, improvement in therapy of these patients

will directly influence total survival rates. 7 of 11 patients with FHF caused by hepatitis B received lamivudine analogue to 8 of 24 patients with acute (non-fulminant) hepatitis B. None of the patients with acute hepatitis B developed FHF and none of the patients with fulminant hepatitis B died but 3 patients still required liver transplantation. Part of these data were published in a recent multicenter observation, indicating that lamivudine is safe in patients with severe acute or fulminant hepatitis B, leading to fast recovery with the potential to prevent liver failure and liver transplantation when administered early enough [16].

Excellent results were also obtained in the paracetamol group due to N-acetylcystein 17-19 treatment. In 6 patients a diagnosis of paracetamol overdose was made, five patients developed acute hepatitis and 1 patient developed FHF. All of them were treated with N-acetylcystein and none of 5 patients with severe hepatitis developed fulminant hepatitis and one patient with FHF could be withdrawn from the transplantation list.

Differences in the outcome may also reflect a change in the spectrum of diseases. In the previous analysis, we had more patients with toxic etiologies (50%) and a patient with Wilson's disease, which were associated with a poor outcome.

Viral infections are the most prominent causes of FHF in our collective. Most of them are induced by hepatitis B, followed by hepatitis A infection, an observation which is similar to other collectives [20-24]. In our series patients with fulminant hepatitis A had a very good outcome without any death nor liver transplantation, comparable with data by others [8, 25, 26]. None of our patients had a fulminant hepatitis C, which is only very rarely seen as the cause of fulminant hepatitis in Europe or USA [27-29], in contrast to Asia, where more cases of fulminant hepatitis C are described [30-32].

Furthermore, improved survival rates may also result from increased experience in the complex management of patients with FHF. This includes management of infectious complications, hepatic encephalopathy, metabolic disorders, renal failure, substitution of coagulation factors as well as catecholamines, and indication and management of liver transplantation.

We also analyzed all patients which were hospitalized for severe non-fulminant hepatitis in the hope to find new markers to differentiate between good and poor outcomes. However, we could not find new parameters to distinguish between these groups, demonstrating once again that a careful clinical observation is indispensable in these patients with imminent hepatic failure.

REFERENCES

1. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet. 1993; 342:273-5.
2. Trey C, Davidson CS. The management of fulminant hepatic failure. Prog Liver Dis. 1970; 3:282-98.
3. Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. Semin Liver Dis. 1986; 6:97-106.
4. O´Grady J, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; 97:439-45.
5. Bernuau J, Samuel D, Durand F, et al. Criteria for emergency liver transplantation in patients with acute viral hepatitis and factor V (FV) below 50% of normal: a prospective study. Hepatology 1991; 14:49A.
6. Paar WD, Muller A, Spengler U, et al. [Progress of acute liver failure and indications for liver transplantation]. Dtsch Med Wochenschr. 1998; 123:549-55.
7. Hoofnagle JH, Carithers RL, Jr., Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. Hepatology. 1995; 21:240-52.
8. Schiodt FV, Atillasoy E, Shakil AO, et al. Etiology and outcome for 295 patients with acute liver failure in the United States. Liver Transpl Surg. 1999; 5:29-34.
9. Ascher NL, Lake JR, Emond JC, Roberts JP. Liver transplantation for fulminant hepatic failure. Arch Surg. 1993; 128:677-82.
10. Brems JJ, Hiatt JR, Ramming KP, Quinones-Baldrich WJ, Busuttil RW. Fulminant hepatic failure: the role of liver transplantation as primary therapy. Am J Surg. 1987; 154:137-41.
11. Devictor D, Desplanques L, Debray D, et al. Emergency liver transplantation for fulminant liver failure in infants and children. Hepatology. 1992; 16:1156-62.
12. Bismuth H, Samuel D, Castaing D, et al. Orthotopic liver transplantation in fulminant and subfulminant hepatitis. The Paul Brousse experience. Ann Surg. 1995; 222:109-19.
13. Peleman RR, Gavaler JS, Van Thiel DH, et al. Orthotopic liver transplantation for acute and subacute hepatic failure in adults. Hepatology. 1987; 7:484-9.
14. Rakela J, Perkins JD, Gross JB, Jr., et al. Acute hepatic failure: the emerging role of orthotopic liver transplantation. Mayo Clin Proc. 1989; 64:424-8.
15. Vickers C, Neuberger J, Buckels J, McMaster P, Elias E. Transplantation of the liver in adults and children with fulminant hepatic failure. J Hepatol. 1988; 7:143-50.
16. Tillmann HL, Hadem J, Leifeld L, et al. Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. J Viral Hepat. 2006; 13:256-63.
17. Makin AJ, Wendon J, Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987-1993). Gastroenterology. 1995; 109:1907-16.
18. O'Grady JG. Paracetamol-induced acute liver failure: prevention and management. J Hepatol. 1997; 26:41-6.
19. Wendon JA, Ellis A, Williams R. Management of paracetamol poisoning. Lancet. 1995; 346:1236.
20. Fagan EA, Harrison TJ. Exclusion in liver by polymerase chain reaction of hepatitis B and C viruses in acute liver failure attributed to sporadic non-A, non-B hepatitis. J Hepatol. 1994; 21:587-91.
21. Fernandez Hernandez JA, Robles Campos R, Hernandez Marin C, et al. [Fulminant hepatic failure and liver transplantation. Experience of the Hospital Virgen de la Arrixaca]. Gastroenterol Hepatol. 2003; 26:333-40.
22. Papaevangelou G, Tassopoulos N, Roumeliotou-Karayannis A, Richardson C. Etiology of fulminant viral hepatitis in Greece. Hepatology. 1984; 4:369-72.
23. Takahashi Y, Kumada H, Shimizu M, et al. A multicenter study on the prognosis of fulminant viral hepatitis: early prediction for liver transplantation. Hepatology. 1994; 19:1065-71.
24. Williams R, Wendon J. Indications for orthotopic liver transplantation in fulminant liver failure. Hepatology. 1994; 20:S5-10S.
25. Boker KH. [Acute liver failure]. Internist (Berl). 2001; 42:545-54, 556-62.
26. Rezende G, Roque-Afonso AM, Samuel D, et al. Viral and clinical factors associated with the fulminant course of hepatitis A infection. Hepatology. 2003; 38:613-8.

27. Feray C, Gigou M, Samuel D, et al. Hepatitis C virus RNA and hepatitis B virus DNA in serum and liver of patients with fulminant hepatitis. Gastroenterology. 1993; 104:549-55.
28. Liang TJ, Jeffers L, Reddy RK, et al. Fulminant or subfulminant non-A, non-B viral hepatitis: the role of hepatitis C and E viruses. Gastroenterology. 1993; 104:556-62.
29. Theilmann L, Solbach C, Toex U, et al. Role of hepatitis C virus infection in German patients with fulminant and subacute hepatic failure. Eur J Clin Invest. 1992; 22:569-71.
30. Yoshiba M, Dehara K, Inoue K, Okamoto H, Mayumi M. Contribution of hepatitis C virus to non-A, non-B fulminant hepatitis in Japan. Hepatology. 1994; 19:829-35.
31. Chu CM, Sheen IS, Liaw YF. The role of hepatitis C virus in fulminant viral hepatitis in an area with endemic hepatitis A and B. Gastroenterology. 1994; 107:189-95.
32. Wu JC, Chen CL, Hou MC, Chen TZ, Lee SD, Lo KJ. Multiple viral infection as the most common cause of fulminant and subfulminant viral hepatitis in an area endemic for hepatitis B: application and limitations of the polymerase chain reaction. Hepatology. 1994; 19:836-40.

Received: July 4, 2007 / Accepted: January 7, 2008

Address for correspondence:
PD Dr. med. Ludger Leifeld
Evangelisches Krankenhaus Köln-Kalk
Buchforststrasse 2
51103 Köln
Germany
E-mail: l.leifeld@gmx.de
Tel.: ++49-221/8289-0

Prof. Dr. med. Ulrich Spengler
Department of Internal Medicine I
University of Bonn
Sigmund-Freud-Straße 25
53105 Bonn
Germany
Tel.: ++49-228/287-5259
Fax: ++49-228/287-4323
E-mail: ulrich.spengler@ukb.uni-bonn.de