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Fatal hepatic decompensation associated with interferon alfa

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Interferon alfa is the most promising treatment for chronic viral hepatitis, suppressing viral replication in about 30% of patients with chronic hepatitis B or C.[1,2] In patients with cirrhosis interferon alfa may improve the outcome of the disease and obviate the need for liver transplantation.[3] Inhibition of viral replication in chronic hepatitis B is usually accompanied by a transient rise in the activities of aminotransferases. This inflammatory exacerbation may cause hepatic decompensation in cirrhotic patients. We report on patients with chronic viral hepatitis who died of hepatic decompensation during or shortly after interferon alfa treatment.

Case reports

After a patient with chronic hepatitis B in our institute exhibited a flare of hepatitis during interferon alfa treatment and died we studied the frequency and clinical aspects of fatal hepatic decompensation related to interferon alfa treatment. We sent a questionnaire to 19 European centres with considerable experience of interferon alfa treatment for viral hepatitis. Sixteen hospitals from nine countries responded. These centres had treated 2490 patients with chronic viral hepatitis with interferon alfa. We studied cases in which the patient had a fatal aggravation of liver disease during or less than two months after interferon alfa treatment. Eight cases from five hospitals were reported; the table gives details of these cases plus our case.

Histological examination before treatment showed that all the patients had chronic active hepatitis with cirrhosis. Four had no signs of hepatic decompensation (ascites, jaundice, encephalopathy, or variceal bleeding) before treatment. Clinical deterioration occurred in the first three months of treatment in seven cases. In cases 7 and 8 the scheduled course of treatment was completed with clearance of viral DNA, but liver failure developed two and eight weeks later. Five patients' aminotransferase activities more than doubled during treatment. No apparent reason for the liver failure other than interferon alfa treatment could be detected in any of the patients.

Comment

Although these cases were selected from a large number in which interferon alfa was given, they suggest that the drug can dangerously aggravate liver disease and that caution is needed in treating cirrhotic patients. A relation between liver failure and interferon alfa seems probable in the patients who did not have hepatic decompensation before treatment. The deaths of patients who showed signs of decompensated liver disease before treatment might have been due to spontaneous progression of the disease and cannot be linked unequivocally to the interferon treatment.

Most of the patients developed ascites, jaundice, and encephalopathy that progressed even after interferon alfa was stopped. Since five of the patients received <10 MU interferon/week fatal hepatic decompensation was not restricted to high dosages of the drug. Relatively late discontinuation of treatment could be a reason for the unfavourable outcome in some cases.

There are several possible explanations for a link between interferon alfa and fatal hepatic injury. Interferon alfa enhances lysis mediated by the immune system of hepatocytes infected with hepatitis B virus,

Details of patients with hepatitis who developed fatal liver failure after interferon alfa treatment

Case No	Age and sex	Type or hepatitis	Signs of decompensation before treatment	Dose and duration of treatment	Type of interferon	Signs of decompensation during treatment	Serum values: AST (U/l)	Serum values: Bilirubin (μmol/l)	Serum values: Albumin (g/l)	HBeAg seroconversion	Cause of death
1	62M	B	None	5 MU thrice weekly for 12 weeks	Recombinant alfa-2b	Ascites, jaundice, encephalopathy	244	648	43	Yes	Liver failure
2	41M	B (mutant)	None	3 MU thrice weekly for 3 weeks	Recombinant alfa-2b	Ascites, jaundice, encephalopathy	302	680	28	NA	Liver failure
3	60F	C	None	10 MU trice weekly for 11 weeks	Recombinant alfa-2b	Ascites, jaundice, encephalopathy	76	410	28	NA	Liver failure
4	62M	B	None	5 MU daily for 8 weeks	Recombinant alfa-2b	Ascites, jaundice	394	226	26	No	Variceal bleeding
5	44M	B	Ascites	5 MU daily for 11 weeks	Recombinant alfa-2a	Ascites, jaundice, encephalopathy	79	88	27	No	Variceal bleeding
6	44M	B/C	Ascites, jaundice	3 MU thrice weekly for 10 weeks	Lymphoblastoid	Ascites, jaundice, encephalopathy	289	272	28	NA	Liver failure, hepatorenal syndrome, peritonitis
7	70M	B	Ascites, variceal bleeding, encephalopathy	2 MU thrice weekly for 24 weeks	Recombinant alfa-2b	Ascites, encephalopathy	9	111	34	Yes	Liver failure
8	36M	B	Ascites	2 MU thrice weekly for 16 weeks	Recombinant alfa-2b	Ascites, peritonitis	16	52	27	Yes	Variceal bleeding
9	53M	B	Ascites, hepatocellular carcinoma	2 MU thrice weekly for 3 weeks	Recombinant alfa-2b	Ascites, jaundice, encephalopathy	500	171	29	No	Liver failure

AST=Aspartate aminotransferase; HBeAg=Hepatitis B e antigen; NA=Not applicable.

resulting in a transient inflammatory exacerbation, which could be lethal in a liver with limited residual capacity.[4] Other possible explanations are that interferon alfa is directly toxic to hepatocytes[5] and that it induces autoimmune chronic active hepatitis.

Despite the dangers of fatal decompensation, we think that interferon alfa should be considered for treating patients with cirrhosis. Loss of viral replication by interferon can lead to a substantial regression of liver disease and probably prolonged survival.[3] In cases in which liver transplantation remains the only option, such a suppression of viral activity may reduce the risk of infection of the graft. Patients likely to develop hepatic decompensation who receive interferon alfa must, however, be monitored closely by an experienced hepatologist, preferably in a centre with facilities for liver transplantation.

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ONE HUNDRED YEARS AGO

FADS OF MEDICAL MEN.

Readers of Mr. Gosse's masterly story of *Narcisse* have felt again how real a terror was witchcraft to our forefathers, and not a terror only but, indeed, a grim and real power of evil also. Mr. Ernest Hart, Professor Horsley, and others, in exposing the falsehoods of modern witches, show the more clearly the power of "suggestion" as a factor in the production of changes in living function for good or ill. We begin to think that the curses of the hag probably did wither up the hagridden, after all. Our fathers burned their witches—a plain and short way with them which had its advantages; we cannot burn ours, but the literary pillory may serve our turn. Yet so interwoven are good and evil that some witchery still holds a place for good in our therapeutics. Dr. Cyrus Edson, in the *North American Review* for the current month, reminds those who prematurely pride themselves on the virtues of some new remedy, that all new remedies do good—for a time; the physician who persuades his patient of the virtues of his means has half cured him already. A successful physician is well convinced of the beneficence of his own work, and rightly so, says Dr. Edson; in this the physician is not wrong, but he is sometimes mistaken in his inference that his success lies in the matter of his prescriptions. A cheery, hopeful assurance buoys up the sinking life, and, as the dominant "fad" of the moment inspires both doctor and patient, the orbit of function under this inspiration lurches round again towards its proper equilibrium. The sick man who "gives in" dies; he who has faith and confidence recovers rather. But if so much of our professional success is by "faith cure," how shall it fare with a "faithless generation?" Perhaps there is never such a generation; perhaps every generation is faithful—after its kind! (*BMJ* 1893;i:595.)

CANINE HYGIENE.

We have received from Mr. Everett Millais a copy of a letter addressed by him to the Committee of the Kennel Club, resigning his membership of the club. The cause of his resignation is one of no little importance to animal hygiene. He and a few other enlightened dog-owners have for some years waged warfare against the utter disregard of hygiene at dog shows. Infectious animals, it appears, are admitted, and the benching, which may be moved about from show to show, is not disinfected. Distemper is largely spread by shows. Mr. Chaplin, when appealed to as Minister of Agriculture, expressed the opinion that the matter was rather one for the Kennel Club than for the Legislature, while, in his other capacity as an M.F.H., who had lost 100 dogs from distemper in one year, he sympathised with the proposal to enforce disinfection and the exclusion of infected dogs. The Kennel Club, there is good reason to believe, might work a great reform by a stroke of the pen; but it appears unwilling to move. Inaction cannot be held to be due to want of knowledge, and we are at a loss to conceive the arguments by which it defends itself from being responsible by this neglect for the infliction of more suffering on dogs and more deaths among dogs in the course of a year than have been produced in the cause of scientific research in a generation. (*BMJ* 1893;i:140.)