CASE REPORTS

Alcoholic hepatitis—the case for intensive management

James O'Beirne, David Patch, Steve Holt, Mark Hamilton, Andrew K Burroughs

Abstract

Alcoholic hepatitis is a common condition with a high mortality. Although treatment options for established alcoholic hepatitis are limited, many of the complications of this condition are preventable. This case report and discussion illustrate the important role of early diagnosis and intervention in this patient group. Important management points are stressed to aid physicians who may encounter this condition rarely.

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The clinical syndrome of alcoholic hepatitis may be asymptomatic. However, in severe forms it is a life threatening condition encompassing jaundice, and ascites, renal failure, gastrointestinal bleeding, increased risk of infection, and encephalopathy. Mortality rates in severe alcoholic hepatitis can be as high as 58% acutely, rising to 78% at one year in some studies.¹ The Royal Free Hospital sees 20–30 patients a year with severe alcoholic hepatitis, many of these referred from district general hospitals.

Despite the lack of a proved, effective, specific treatment, except possibly in a subset of patients who may benefit from corticosteroids, correct management of these patients from the outset may prevent some of the above complications.

The most severe complications of alcoholic hepatitis, in particular the hepatorenal syndrome, are often preventable but often very difficult to treat once established.

The following case report illustrates the importance of early proactive management of the problems highlighted above, including the need for early referral to a liver unit. This paper attempts to illustrate the clinical features and complications of alcoholic hepatitis, and to give physicians who see this condition less commonly than in a liver unit, clear management guidelines.

Case report

A 39 year old man, with a greater than 10 year history of alcohol misuse, was admitted to the referring hospital due to the development of abdominal distension. He had no previous admissions with alcohol related problems.

On examination, he was jaundiced with multiple spider naevi and palmar erythema. The liver was enlarged and tender. A moderate amount of ascites was present in the abdomen. Initial blood tests showed urea 1.1 mmol/l (3.0–6.5), creatinine 44 µmol/l (60–120), bilirubin 212 µmol/l (5–17), alanine aminotransferase (ALT) 65 IU/l (5–40), aspartate aminotransferase (AST) 124 IU/l (5–40), albumin 31 g/l (35–50), and alkaline phosphatase 249 IU/l (35–130). The prothrombin time was prolonged at 19 seconds (control 14.2) and full blood count showed thrombocytopenia, but normal haemoglobin and white cell count.

He was fluid restricted to one litre per day and given spironolactone 50 mg once daily as treatment for his ascites. Three days later, he absconded from the ward.

He was found at home in a confused state and was readmitted to the same hospital. Treatment for alcohol withdrawal was started with a standard reducing course of chloridiazepoxide. On day 9 of his admission, he had become drowsy and further ascites had accumulated, chlorthalidone was reduced and the spironolactone increased to 100 mg/day, with the addition of frusemide (furosemide) 40 mg once daily.

Blood tests on day 10 showed urea 23.1 mmol/l, creatinine 527 µmol/l, and sodium 127 mmol/l. His peripheral white blood cell count was $22.1 \times 10^9/l$ and cefotaxime 1 g, eight hourly, was started. He was referred to the Royal Free Hospital Liver Unit for further management.

On admission to our unit, he was markedly jaundiced and in grade II encephalopathy. Multiple spider naevi and palmar erythema were noted. He was clearly malnourished with marked loss of muscle mass, anthropometric measurements confirming a mid-arm circumference of 22 cm (<5th centile). Temperature was 37.5°C and he was clinically dehydrated. Blood pressure was 90/60 mm Hg. The liver was enlarged 8 cm below the costal margin with no bruit and there was moderate ascites. Initial blood tests showed urea 27.8 mmol/l, creatinine 607 µmol/l, AST 106 IU/l, ALT 37 IU/l, and bilirubin 675 µmol/l. The prothrombin time was prolonged at 22 seconds and he was thrombocytopenic.

Initial management consisted of withdrawal of diuretics and volume replacement with 4.5% human albumin. A nasogastric tube was placed and enteral feeding started. Infusions of renal dose dopamine (2.5 µg/kg/min) and

University
Department of
Medicine, Royal Free
Hospital, London, UK
J O'Beirne
D Patch
S Holt
M Hamilton
A K Burroughs

Correspondence to:
Dr James O'Beirne, Dicker
Ward, Eastbourne District
General Hospital, Kings
Drive, Eastbourne, East
Sussex BN21 2UD, UK
(email: jamesobrn@aol.com)

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N-acetylcysteine (100 mg/kg over 16 hours) were started. Because of persistent oliguria, hypotension, and worsening renal impairment terlipressin 1 mg, six hourly, was started after a test dose. Encephalopathy was treated with lactulose and phosphate enemas. Cultures of blood, urine, and ascites were obtained and cefotaxime was continued.

With this management, his encephalopathy resolved, as did oliguria with a concomitant fall in serum creatinine. Transjugular liver biopsy confirmed severe alcoholic hepatitis with cirrhosis and he was placed on prednisolone 40 mg once a day. He continued to improve, terlipressin, dopamine, and *N*-acetylcysteine eventually being discontinued. He was discharged well, with normal renal function, 32 days after his initial admission.

He was seen regularly thereafter in the outpatient department and given counselling and support. With total abstinence, further improvement in liver function could be expected up to one year. Unfortunately, the patient began drinking again and his clinical condition deteriorated with further encephalopathy and renal failure. This deterioration proved irreversible and he died three months after his initial admission.

Discussion

This management of this patient highlights some of the dilemmas that occur in patients with alcoholic hepatitis. In this case, the initial use of diuretics may have contributed to the development of hepatorenal syndrome. As is often the case, this was the patient's first presentation with alcoholic hepatitis.

Physicians who do not usually see this condition may not be aware of the grave significance of jaundice in the alcohol misuser. In the presence of active drinking this usually represents clinical alcoholic hepatitis. The other setting in which jaundice develops is severe end stage cirrhosis. Either of these conditions are life threatening. The most important intervention in alcoholic hepatitis is complete and indefinite abstinence from alcohol. In patients with cirrhosis, liver function may improve with abstinence. Certainly, mortality rates are much higher in patients who continue to misuse alcohol. Progression to cirrhosis may be prevented in the non-cirrhotic group by abstinence.

Initial management steps are shown in box 1.

INITIAL ASSESSMENT

The diagnosis of alcoholic hepatitis is suggested in jaundiced patients who have the following features.

- They have usually been drinking alcohol until the time of admission.
- Stigmata of chronic alcohol misuse may be present—for example, spider naevi.
- Hepatic bruit may be heard.
- The neutrophil count may markedly raised, often $>20 \times 10^6$.
- Patients may be febrile.
- Transaminases are raised (but may be normal), showing a more marked increase of the AST in comparison with ALT. (The

AST is often only 2–3 times normal, increases of more than 10 times normal are not consistent with alcoholic hepatitis.)

- There is often a relative reduction in food intake in the months/weeks before admission.

PROGNOSTIC ASSESSMENT

Maddrey has described an index of severity in patients with alcoholic hepatitis.² The discriminant function (DF) is calculated as follows.

$$\text{DF} = (\text{patient's prothrombin time} - \text{control}) \times 4.6 + (\text{bilirubin } (\mu\text{mol/l})/17.1)$$

The DF serves as a prognostic index, those with a DF >32 have much greater risk of mortality and may benefit from steroids. The DF is easy to calculate and should be part of the initial assessment in all patients where alcoholic hepatitis is suspected. Other factors such as C reactive protein,³ cytokines,⁴ and markers of lipid peroxidation⁵ may also have a role as initial prognostic factors, but currently are only useful as research tools.

FLUID MANAGEMENT

All patients admitted with a clinical diagnosis of alcoholic hepatitis should have an internal jugular line inserted in order to ensure that they are volume replete. The presence of a coagulopathy or thrombocytopenia is not a contraindication to the insertion of an internal jugular line, but the subclavian approach should be avoided. Normal saline should be avoided, as these patients are unable to deal with the salt load. Human albumin solution, 4.5%, is our plasma expander of choice, possibly with the additional use of salt poor (20%) albumin.

MANAGEMENT OF ALCOHOL WITHDRAWAL

A history of alcohol abuse, dependency, and a history of withdrawal related symptoms, should be sought carefully from the patient and the relatives. It should be assumed that those patients who are actively drinking until the time of admission will require treatment for withdrawal. There is no ideal sedative in patients with alcohol withdrawal. Diazepam and chlormethiazole are the agents with which there is most experience. Chlormethiazole has

Box 1: Initial management steps in alcoholic hepatitis

- Suspect the diagnosis in all jaundiced alcohol misusers.
- Calculate the discriminant function index on admission.
- Avoid diuretics and ensure adequate volume replacement.
- Institute nasogastric feeding early to avoid deterioration in liver function.
- Broad spectrum antibiotics early (after cultures of blood, urine, and ascites).
- Daily tests of renal function and prothrombin time.

a shorter half life than diazepam and is our drug of choice. Benzodiazepams do have the advantage that oversedation can be reversed.

Patients with severe withdrawal syndromes may require intravenous chlormethiazole, ideally in an intensive therapy unit/high dependency unit setting.

MONITORING OF BLOOD TESTS

These patients are critically ill so renal function and electrolytes should be checked at least once daily and the results discussed with a senior member of the medical team. Monitoring of this frequency should prevent the development of undiagnosed renal failure as occurred in the patient we have presented. The prothrombin time is the most important indicator of liver function in this setting. Transaminases are often only mildly raised (2–3 times normal) (AST greater than ALT) and are not of value in determining prognosis. Many patients with alcoholic hepatitis will have a marked neutrophilia secondary to neutrophil chemokine release in the liver, which is an additional aid to diagnosis, but should always raise the possibility of sepsis.

ANTIBIOTICS

Patients with alcoholic hepatitis are at high risk of sepsis. They also commonly have fever, this may relate to the inflammatory process in the liver, and not infection. However, in the presence of fever and/or a neutrophilia we recommend the prompt use of broad spectrum antibiotics, ideally cefotaxime 1 g three times a day after appropriate cultures. Cultures and cell count of any ascitic fluid should always be performed to exclude spontaneous bacterial peritonitis, which has a very high morbidity and mortality.⁶ Fungal prophylaxis may also be given. Control of sepsis is clearly an essential issue as this is an important precipitant of renal failure.⁷

NUTRITION

Early enteral nutrition is a vital part of the management of alcoholic hepatitis for a number of reasons. Firstly, these patients have had a very high calorie intake from alcohol until the time of admission. The abrupt withdrawal of these calories is associated with a deterioration in liver function. We recommend enteral feeding via a fine bore nasogastric tube from the outset in patients who are unable to maintain a calorie intake of more than 2000 calories/day. Our enteral feed of choice is Nepro (Abbott) with 16.6 g of protein/237 ml.

Secondly, the use of enteral feeding allows simplification of fluid management. After the initial resuscitation that may be required, enteral feeding may supply all the fluid and electrolytes that are required. This is important to prevent iatrogenic electrolyte imbalance. Maintenance of fluid balance via the enteral route avoids the need for intravenous catheters, which are a common source of infection in these relatively immunosuppressed patients. The importance of adequate nutrition should not be underestimated; large series have shown that protein energy malnutrition is present in

all patients with a clinical diagnosis of alcoholic hepatitis and that this is an independent risk factor for early mortality.⁸

Many physicians would advocate a low protein diet to avoid or ameliorate hepatic encephalopathy. However, it has been shown that low protein diets in patients with alcoholic hepatitis worsens encephalopathy, and that in patients who can take standard antiencephalopathy medication a high protein diet is well tolerated and improves encephalopathy.⁹

All patients should be given oral and where necessary intravenous thiamine supplementation.

DIURETICS AND MANAGEMENT OF FLUID RETENTION

These patients are unlikely to experience any clinical problems from the accumulation of ascitic fluid during the initial illness. Our clinical practice is not to use any form of diuretic or fluid restriction in patients who are acutely ill with alcoholic hepatitis. The risk of precipitating renal failure is high and maintenance of intravascular volume, even at the expense of fluid retention, is a priority. If ascites becomes tense, painful, or compromises respiration then large volume paracentesis can be performed. To ameliorate the risk of fluid depletion 100 ml of 20% albumin should be infused to replace every two litres of ascites drained.¹⁰ We would recommend that no diuretics be given before referral.

USE OF STEROIDS IN ALCOHOLIC HEPATITIS

Several small trials have suggested that there is a survival benefit for patients treated with prednisolone, though a recent meta-analysis has not confirmed this, and suggests a publication bias has overestimated the likely benefit from steroid use.¹¹ However, this study did not look at the subgroups in whom steroid therapy has been suggested to be beneficial. We recommend steroids in patients in who fulfil the following characteristics.

- Patients are free of sepsis or have received 48 hours of broad spectrum antibiotics if sepsis is present.
- Bleeding should have been controlled for more than 48 hours.
- Patients should have no other contraindications to steroid treatment.
- Discriminant function index >32.

We would recommend that steroids are not started before referral to a liver unit, particularly as this may increase the incidence of sepsis.

ROLE OF LIVER BIOPSY

Liver biopsy is helpful in the management of alcoholic hepatitis, and confirms the diagnosis in patients who are to be treated with steroids. Histology can confirm the presence of alcoholic hepatitis and presence of cirrhosis. Biopsy will also exclude other aetiologies of liver disease such as haemochromatosis and α_1 -antitrypsin deficiency. Due to coagulopathy and ascites, biopsy by the transjugular route may be indicated. The advent of new needles has significantly improved this technique.

ORTHOTOPIC LIVER TRANSPLANTATION

Currently there is no role for liver transplantation in acute alcoholic hepatitis. Liver transplantation can be considered in patients with alcoholic hepatitis and cirrhosis who have failed to improve after a prolonged period of abstinence.

FUTURE THERAPEUTIC OPTIONS

Despite advances in the understanding of the pathogenesis of alcoholic hepatitis, therapeutic options remain disappointingly limited. Calcium channel blockers, which have been shown to be effective in the animal model of alcoholic hepatitis,¹² have been shown to be ineffective in controlled trials.¹³ Other strategies such as anabolic steroids, antifibrotics, and "hepatoprotective" agents have similarly been shown ineffective.

Vasopressin analogues (for example, terlipressin) may be effective in improving renal function in hepatorenal syndrome,^{14 15} however these drugs can have adverse side effect profiles and most patients seem to relapse when the drug is discontinued. Use of *N*-acetylcysteine has become commonplace in a variety of liver diseases. It is largely well tolerated, safe, and has theoretical advantages in terms of its action as an antioxidant and it may improve organ function by increasing oxygen extraction.¹⁶ In a pilot study, we have recently shown that *N*-acetylcysteine may be useful in improving renal function in hepatorenal syndrome caused predominantly by alcoholic liver disease.¹⁷ Since hepatorenal syndrome is associated with a mortality rate in excess of 95%,¹⁸ these therapeutic options deserve more investigation.

In summary, if physicians are aware of the grave significance of jaundice in the actively drinking alcohol misuser, many of the complications of alcoholic hepatitis may be prevented. Patients should be considered by the referring hospital to be as unstable as patients with fulminant liver failure. Early discussion with, and, referral to a regional liver unit, if appropriate, is recommended for these patients. The most important therapeutic intervention is complete abstinence from alcohol. This may be followed by orthotopic liver transplantation, if liver function does not recover and the patient is otherwise suitable.

The above case illustrates the success that can be achieved with the aggressive management of alcoholic hepatitis. At present it is impossible to predict which patients will not abstain from alcohol, therefore we recommend all patients should be offered intensive management in the first instance, followed by counselling and support to prevent relapse. Whether this should be repeated in the scenario of continued drinking remains an ongoing debate.

- 1 Morgan MY. The treatment of alcoholic hepatitis. *Alcohol* 1996;31:117-34.
- 2 Maddrey WC. Alcoholic hepatitis: pathogenesis and approaches to treatment (review). *Scand J Gastroenterol* 1990; 175:118-30.
- 3 Gupta S, Slaughter S, Akrivadias EA, et al. Serial measurement of serum C-reactive protein facilitates evaluation in alcoholic hepatitis. *Hepato-gastroenterology* 1995;42: 516-21.
- 4 Maltby J, Wright S, Bird G, et al. Chemokine levels in human liver homogenates: association between GRO alpha and histopathological evidence of alcoholic hepatitis. *Hepatology* 1996;24:1156-60.
- 5 Aleynik SI, Leo MA, Aleynik MK, et al. Increased circulating products of lipid peroxidation in patients with alcoholic liver disease. *Alcohol Clin Exp Res* 1998;22:192-6.
- 6 Navasa M, Rimola A, Rodes J. Bacterial infections in liver disease. *Semin Liver Dis* 1997;17:323-33.
- 7 Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepato-renal syndrome in cirrhosis. *Hepatology* 1996;23:164-76.
- 8 Mendenhall CL, Moritz TE, Roselle GA, et al. Protein energy malnutrition in severe alcoholic hepatitis: diagnosis and response to treatment. *J Enteral Parenteral Nutr* 1995;19:258-65.
- 9 Morgan TR, Moritz TE, Mendenhall CL, et al. Protein consumption and hepatic encephalopathy in alcoholic hepatitis. *J Am Coll Nutr* 1995;14:152-8.
- 10 Gines A, Fernandez-Esparrach G, Monescillo A, et al. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. *Gastroenterology* 1996;111:1002-10.
- 11 Christensen E, Gluud C. Glucocorticoids are ineffective in alcoholic hepatitis: a meta-analysis adjusting for confounding variables. *Gut* 1995;37:113-8.
- 12 Iimuro Y, Ikejima K, Rose ML, et al. Nimodipine, a dihydropyridine-type calcium channel blocker, prevents alcoholic hepatitis caused by chronic intragastric ethanol exposure in the rat. *Hepatology* 1996;24:391-7.
- 13 Bird GL, Prach AT, McMahon AD, et al. Randomised controlled double-blind trial of the calcium channel antagonist, amlodipine in the treatment of acute alcoholic hepatitis. *J Hepatol* 1998;28:194-8.
- 14 Ganne-Carrie N, Hadengue A, Mathurin P, et al. Hepatorenal syndrome. Long term treatment with terlipressin as a bridge to liver transplantation. *Dig Dis Sci* 1996;41:1054-6.
- 15 Cervoni JP, Lecomte T, Cellier C, et al. Terlipressin may influence the outcome of hepato-renal syndrome complicating alcoholic hepatitis. *Am J Gastroenterol* 1997;92:2113-4.
- 16 Devlin J, Ellis AE, McPeake J, et al. *N*-acetylcysteine improves indocyanine green extraction and oxygen transport during hepatic dysfunction. *Crit Care Med* 1997;25: 236-42.
- 17 Holt S, Goodier D, Marley R, et al. Improvement in renal function in hepatorenal syndrome with *N*-acetylcysteine. *Lancet* 1999;353:294-5.
- 18 Moore K. The hepatorenal syndrome. *Clin Sci* 1997;92: 433-43.