ELSEVIER

The European Journal of Heart Failure 6 (2004) 561–565

The European Journal of Heart Failure

www.elsevier.com/locate/heafai

Short report

Acute hypoxic hepatitis ('liver shock'): still a frequently overlooked cardiological diagnosis

Caroline Denis[a], Caroline de Kerguennec[b], Jacques Bernuau[b], Florence Beauvais[a], Alain Cohen Solal[a,*]

[a] *Service de Cardiology, Hôpital Beaujon, AP-HP, 100 boulevard du Général Leclerc, 92110, Clichy, France*
[b] *Service de Hepatology, Hôpital Beaujon, AP-HP, 100 boulevard du Général Leclerc, 92110, Clichy, France*

Received 16 January 2003; received in revised form 20 September 2003; accepted 12 December 2003

Abstract

The diagnosis of acute hypoxic hepatitis remains problematic. We describe a series of 14 patients who were initially hospitalized in an hepatic care unit with a diagnosis of fulminant hepatitis, and were subsequently found to have acute hypoxic hepatitis ('liver shock') secondary to heart failure. A diagnostic algorithm is proposed.

Keywords: Acute hypoxic hepatitis; Heart failure

1. Introduction

Acute hypoxic hepatitis—sometimes still described as liver shock—is generally defined on the basis of histologic evidence of centrolobular hepatocytic necrosis [1]. It usually results from severe, although sometimes transient, circulatory failure [2]. Controversy remains about the respective roles of acute low hepatic blood flow ('forward failure') and venous congestion ('backward failure') in its pathophysiology, and about whether or not both mechanisms must be present simultaneously for acute hypoxic hepatitis to occur [3–6].

The diagnosis of acute hypoxic hepatitis is usually based on a combination of severe cardiac clinical signs (signs of congestion and low blood flow) and major hepatic disorders. It is generally confirmed by specialized cardiologic investigations, a favourable response to cardiologic treatment and in some cases, liver biopsy.

Diagnosis is generally considered to be easy, and the topic is generally not addressed in major books of cardiology. This diagnosis, in fact, still remains problematic, as illustrated by the present series of 14 consecutive patients who were admitted to the intensive care unit of the hepatology department of the Beaujon University Hospital over a three-year period for suspected fulminant hepatitis. The final diagnosis was acute hypoxic hepatitis, leading to the transfer of the patients to our cardiac intensive care unit. These patients had signs of acute hepatitis but none of them had cardiogenic shock or pulmonary edema. We propose a diagnostic algorithm that should help to avoid delays in diagnosis and appropriate cardiac treatment of the heart failure of these patients.

2. Study population

The four women and ten men were hospitalized between 1997 and 1999. Their mean age was 56 ± 10 years, and their socioeconomic status was generally poor. Six patients had a known cardiac problem, two were on anti-hypertensive treatment, one was receiving treatment for angina pectoris, and five had no known cardiac history. Only three patients had a previous history of heart failure. Four had taken drugs with known hepatotoxic effects. The hepatology department was often the second or third ward in which the patient had been hospitalized: five patients were referred from another teaching hospital, four from a general hospital, three from a private clinic, and two from a medical emergency room. The interval between initial hospitalization and arrival in our cardiology unit ranged from 1 to 8 days (mean 4 days). The

* Corresponding author. Tel.: +33-1-408-75785; fax: +33-1-40870838.
E-mail address: alain.cohen-solal@bjn.ap-hop-paris.fr (A. Cohen Solal).

1388-9842/$ - see front matter © 2004 European Society of Cardiology. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.ejheart.2003.12.008

diagnosis was generally corrected within a few hours in the liver unit. It is noteworthy that two patients had already been examined by a cardiologist—who did not consider the diagnosis of acute hypoxic hepatitis—before their transfer to the liver unit.

3. Clinical manifestations

Gastrointestinal manifestations generally predominated, with nausea, vomiting and right hypochondrial pain in eight cases each; and acute diarrhea in three cases. Six patients had patent jaundice and 11 had markedly altered general status. In the preceding days, six patients had complained of increasing breathlessness and one of chest pain. Eight patients had no cardiac symptoms before their hospitalization.

Physical examination always showed marked hepatomegaly, a sign that is generally absent in fulminant hepatitis (Table 1). The liver was tender in seven patients, and seven patients had jugular turgescence or hepatojugular reflux. Ascites was present in five cases and lower-limb edema in eight cases. Four patients had encephalopathy. All the patients had relatively low blood pressure (mean 100/60 mmHg). Mean heart rate was 100 bpm: in fact, seven had a heart rate >100/min and two had bradycardia (related to hyperkalaemia and right ventricular infarct). A systolic murmur was noted in five patients. Five patients had pulmonary rales or pleural effusion. According to our inclusion criteria, none had signs of cardiogenic shock or pulmonary edema.

Laboratory tests (Table 1 and Fig. 1) showed marked hepatic abnormalities, which in most cases, were probably the main reason for transfer to the liver unit. Major hepatic cytolysis was a consistent finding: transaminase activity was 74 times the normal on average (max: 313 N). Alkaline phosphatase activity and bilirubin levels were 3 and 4 times the normal value, respectively. Thrombocytopenia was found in 10 patients. All but one of the patients had a prothrombin time below 50% of normal, and the mean factor V level on admission was very low (27%). Hypoxemia was found in four of the eight patients in whom blood gases were analyzed. Finally, 11 patients had renal impairment on admission, with a mean creatinine of 185 μmol/l.

4. Specific investigations

Only seven patients had an abdominal ultrasound scan. Five of these patients had dilation of the suprahepatic veins and inferior vena cava, revealing heart failure. Hepatic echography was normal in the other two cases.

All the patients had electrocardiographic abnormalities, consisting of sinus tachycardia in four cases, bradycardia in two cases, microvoltage (owing to abundant pericardial effusion) in one case, left ventricular hypertrophy in three cases, bundle branch block in four cases, repolarization abnormalities in three cases, and signs of myocardial infarction (right ventricle) in one case. Four patients had atrial fibrillation and one had a paced rhythm. These findings confirmed the recently reported excellent negative predictive value of ECG in heart failure [7]. Chest radiography showed cardiomegaly in 10/14 cases, pulmonary vascular congestion in seven cases, and pleural effusion in five cases.

All the patients underwent Doppler echocardiography, often after some delay, in the hepatic or cardiac intensive care unit; the findings were always abnormal. Left ventricular systolic function was altered in 13/14 patients, with a left ventricular ejection fraction of less than 50% (mean 29%); the remaining patient had a large infarct involving the right ventricle. Marked pulmonary arterial hypertension (mean 65 mmHg for systolic pressure) was found in seven patients. Echocardiography always showed the cause of acute hypoxic hepatitis, namely dilated cardiomyopathy in five cases, ischemic cardiopathy in three cases, hypertrophic cardiomyopathy in three cases, and cardiac tamponade, aortic stenosis and acute myocarditis in one case each.

Right heart catheterization was performed in five cases, and confirmed the very low cardiac index (1.7 l/min/m^2 on average). Three patients had needle biopsy of the liver, which always showed centrolobular hepatocytic necrosis.

5. Treatment and outcome

Medical treatment of heart failure (diuretics in 12 patients, positive inotropes in 12 patients and vasodilators in four patients) was started on admission to the cardiac intensive care unit. One patient was treated by pericardial punction, two by temporary cardiac stimulation, and one patient had an emergency aortic valve replacement. Cardiac signs resolved in every case, after a mean of 5 days. Transaminase activity returned to normal after 7 to 10 days. Two patients died suddenly, one due to severe, uncontrolled heart failure and one due to secondary septicaemia.

6. Discussion

Despite regular review articles on the diagnosis of acute hypoxic hepatitis (‘liver shock’) (mainly in non-cardiological journals) and proposed measures to limit diagnostic errors [4,8], this syndrome remains a major pitfall. Previous studies have mainly involved intensive care units patients with a variety of clinical manifestations. For example, respiratory distress was the most frequent sign in Fuchs’ study [5], while the study published by Henrion et al. [9] involved intensive care units patients with low cardiac output. Hemodynamic signs of circulatory failure rarely predominated in our study, making the diagnosis even less obvious, especially in those patients who had no previous cardiac history [4]. A transient event such as arrhythmia or

Table 1
Clinical and laboratory findings in 14 patients with AHH admitted to an hepatic care unit

N	Age	Cardiac history	Functional signs	Hepato-megaly	Jugular vein turgescence or reflux	Ascitis, Edema	Encepha-lopathy	Arterial pressure	Heart rate	Left heart congestive signs	Transaminases (ASAT/ALAT)	Bilirubin	Alkaline Phosphatases	Prothrombin time	Factor V	Plasma creatinine	Outcome
1	64	Hypertension	Dyspnea, asthenia	+	–	+	0	90/60	130 (supraventricular rhythm)	+	860/680	21	110	14%	35%	160	Death
2	72	Atrial fibrillation, left ventricular hypertrophy	Dyspnea, asthenia	+	+	+	0	80/40	37 (junctional rhythm)	+	600/400	40	102	60	–	449	Death
3	73	Left ventricular dysfunction	Dyspnea, asthénia	+	–	–	0	120/70	100	+	2000/2000	46	46	54	42	143	Favourable
4	53	Dilated cardiomyopathy	Asthenia, vomitis	+	–	–	0	110/60	108	+	3100/1860	127	300	15	16	78	Favourable
5	57	Mitral regurgitation	Dyspnea, asthenia	+	–	+	0	100/80	80	+	841/877	72	106	30	32	136	Favourable
6	20	Dilated cardiomyopathy	Dyspnea, vomitis	+	+	+	0	100/70	100	+	940/1240	55	116	30	32	89	Favourable
7	45	Hypertension	Asthenia	+	–	–	0	140/80	90	–	8176/4278	66	95	26	27	306	Favourable
8	77	Angina pectoris	Asthenia	+	–	+	+(stage I)	100/60	88	+	760/1000	52	95	23	29		Favourable
9	48	–	Dyspnea	+	+	+	0	120/60	150 (Atrial fibrillation)	+	8730/3330	171	242	19	32	87	Favourable
10	64	–	Dyspnea	+	+	+	+(stage II)	110/70	77	+	12 555/5465	97	158	14	21	236	Favourable
11	53	–	Asthenia	+	–	+	0	100/60	90	–	925/1506	46	233	33	17	136	Favourable
12	45	–	Dyspnea	+	–	+	0	110/80	110	+	3279/2348	61	189	32	27	117	Favourable
13	70	–	Vomiting	+	+	–	0	120/70	56	–	3690/4520	28	66	27	21	380	Favourable
14	43	–	Asthenia	+	–	–	0	90/50	100	–	1220/2320	29	247	30	48	100	Favourable

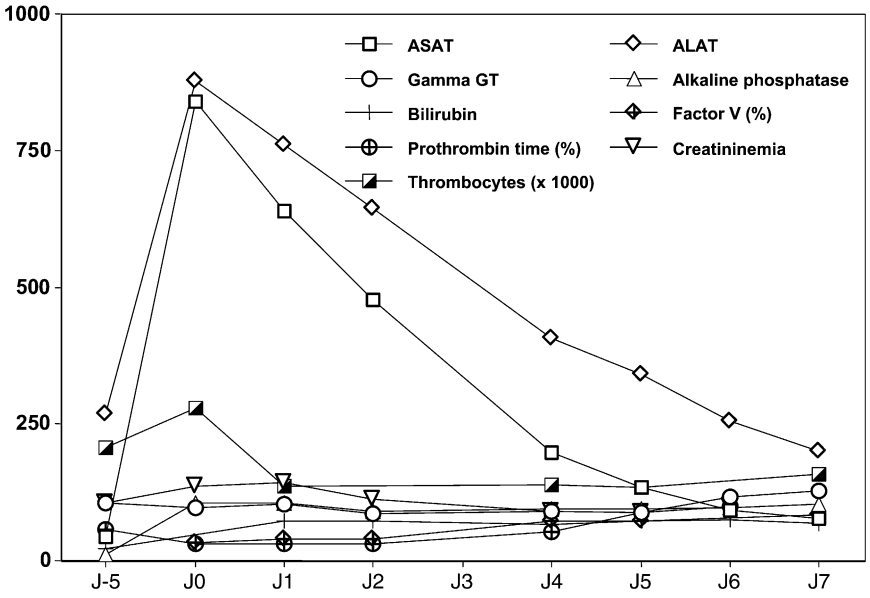

Fig. 1. Evolution of biological variables in a patient with moderately severe acute hypoxic hepatitis. J-5 refers to 5 days before hospitalization; JO to the hospitalization in the hepatic ward and J1 to J7 to the hospitalization in the cardiac ICU.

major hypotension can sometimes cause acute hypoxic hepatitis, hindering retrospective diagnosis [3,10]. The diagnostic delay was particularly striking in our study, especially as all 14 patients were initially hospitalized in highly competent medical services. Most of the patients had a known history of heart disease, but cardiac signs were totally absent in approximately 50% of cases; when present, these signs were sometimes overlooked, possibly owing to the severity of the hepatic signs. In most cases the diagnosis of fulminant hepatitis was probably considered on the basis of marked hepatic cytolysis, even though signs of heart failure had been noted in some patients. While prior intake of hepatotoxic drugs was always taken into account, the patient interview obviously neglected the cardiac history. The diagnosis was usually corrected within hours of admission to the intensive care unit of our hepatology department, thanks mainly to our past experience of such diagnostic errors.

The pathophysiology of acute hypoxic hepatitis remains unclear: nine of our patients did not have clinical signs of raised right venous pressure at least at clinical evaluation and hepatic echography did not reveal dilatation of the supra-hepatic veins of or the inferior vena cava in the two out of the seven patients in whom it was performed. Conversely, seven of the patients had at arrival a systolic arterial pressure greater that 100 mmHg. A systematic hemodynamic evaluation should be performed in these patients to better understand the pathophysiology of the syndrome, knowing, however, that an acute, transient, severe decrease in hepatic blood flow (for example during previous unrecognized arrhythmia) may be overlooked.

In acute hypoxic hepatitis, transaminases can increase to more than 100 times the normal values, in relation with the importance of centro-lobular hepatic necrosis, peaking at 12–24 h and normalizing within 10 days with treatment. Alkaline phosphates and bilirubin increase less. Decreased prothrombin time has an important prognostic value. Other coagulation factors may decrease with the importance of hepatic failure. Thrombopenia, when present, occurs simultaneously with the decrease of the prothrombin time. Importantly, renal failure is found in nearly every case of acute hypoxic hepatitis whereas it occurs in only approximately 30% of the patients with fulminant hepatitis, in association with encephalopathy. Prognosis in our study was better than in the literature (50% mortality) probably because we excluded patients in obvious pulmonary edema or cardiogenic shock and because previous studies enrolled patients from general intensive care units with other co-morbidities.

7. Conclusion

Acute hypoxic hepatitis (‘liver shock’) is still a major diagnostic pitfall. One should remember that a major (even more than 100-fold) elevation of transaminases may not only be due to acute viral or toxic hepatitis, but also to acute hypoxic hepatitis. This latter diagnosis should be seriously considered in patients with (1) past or present cardiac disease (even minimal); (2) electrocardiographic abnormalities (an ECG must be done systematically: our findings suggest that a normal ECG virtually eliminates the diagnosis of acute hypoxic hepatitis); (3) radiographic pulmonary abnormalities (found in about half of all patients with acute hypoxic hepatitis); (4) classical hepatic biochemical abnormalities (marked increase in transaminase activity, contrast-

ing with less severe signs of cholestasis and liver failure); and (5) initial renal impairment, rare in other causes of hepatitis.

In the vast majority of such cases, two examinations rapidly provide the correct diagnosis:

a. abdominal echography is virtually pathognomonic when it shows dilation of the inferior vena cava and suprahepatic veins; and
b. Doppler echocardiography yields the diagnosis.

These examinations should, therefore be undertaken routinely in every patient in whom a diagnosis of fulminant hepatitis is suspected, in particular before liver biopsy.

References

[1] Henrion J, Luxaert R, Colin L, Schmitz A, Schapira M, Heller F. Hépatite hypoxique. Gastroen Clin Biol 1990;14:836–41.
[2] Benhamou J, Foie cardiaque aiguë. In: Benhamou J, editor. Hépatologie clinique. Paris: Flammarion: 1159–64.
[3] Bernuau J. Ischémie hépatique aiguë. La Presse Med 1986;2:80–6.
[4] Henrion J, De Maggt S, Schapira M, Ghillain J, Maisin J, Gerard R, et al. Hypoxic hepatitis: a difficult diagnostic when the cardiomyopathy remains unrecognised and the course of liver enzymes follows an atypical pattern: a report of two cases. Acta Gastro-Ent Belg 1998:385–9 (LXI).
[5] Fuchs S, Bogomolski-Yahalom V, Paltiel O, Ackerman Z. Ischemic hepatitis: clinical and laboratory observations of 34 patients. J Clin Gastroenerol 1998;26:183–6.
[6] Henrion J, Minette P, Colin L, Schapira M, Delannoy A, Heller F. Hypoxic hepatitis caused by acute exacerbation of chronic respiratory failure: a case-controlled, hemodynamic study of 17 consecutive cases. Hepatology 1999;29:427–33.
[7] Cohen-Solal A, Desnos M, Delahaye F, Emeriau JP, Hanania G. A national survey of heart failure in French hospitals. The Myocardiopathy and Heart Failure working group of the French Society of Cardiology, the National College of General Hospital Cardiologists and the French Geriatrics Society. Eur Heart J 2000;21:763–9.
[8] Seeto R, Fenn B, Rockey D. Ischemic hepatitis: clinical presentation and pathogenesis. Am J Med 2000;109:109–13.
[9] Henrion J, Descamps O, Luwaert R, Schapira M, Parfonry A, Heller F. Hypoxic hepatitis in patients with cardiac failure: incidence in a coronary care unit and measurement of hepatic blood flow. J Hepatol 1994;21:696–703.
[10] Shovman O, George J, Shoenfeld Y. Ischemic hepatitis in congestive heart failure after an episode of hypotension. Harefuah 1997;132:459–60.