Histoire naturelle de la cirrhose virale B après une première décompensation en Tunisie

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Medical demography in Tunisia: current situation and perspectives

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RÉSUMÉ

But : Déterminer l'histoire naturelle de la cirrhose virale B après la première décompensation et de dégager les facteurs prédictifs de mortalité.

Méthodes : Etude rétrospective longitudinale incluant 77 cas de cirrhose virale B parmi 192 malades cirrhotiques consécutifs hospitalisés entre 1997 et 2005 pour une première décompensation. Les malades ont été suivis jusqu' à 31 décembre 2006. La probabilité de survie après la première décompensation a été calculée en utilisant la méthode de Kaplan Meier. Les facteurs prédictifs de mortalité ont été déterminés par une analyse uni variée et multi variée en utilisant le modèle de régression de Cox.

Résultats : Il s'agissait de 54 hommes et de 23 femmes d'âge moyen de 54 ±14,9 ans (18-85 ans) hospitalisés pour une première décompensation de cirrhose virale B. Sur un suivi moyen de 24,2 ±21,1 mois, 64% des patients sont décédés. La probabilité de survie après la première décompensation était de 47% à 2 ans et de 22% à 5 ans. Durant le suivi ; l'ascite était la complication la plus fréquente (84 %) suivie de l'encéphalopathie hépatique (38%), de l'hémorragie digestive d'origine variqueuse (34%), de l'ictère (30 %), de syndrome hépato rénal (27 %),de carcinome hépatocellulaire (21 %), et de l'infection péritonéale spontanée (14 %). En analyse uni variée, 4 facteurs étaient prédictifs de mortalité : le score de Child Pugh C (p=0,009), le carcinome hépatocellulaire (p=0,01), un taux de gammaglobulines supérieur à 18g/l (p=0,008) et un taux de prothrombine inférieur à 50% (p=0,02). En analyse multi variée seul un taux de gammaglobuline supérieur à 18g/l était un facteur indépendant prédictif de mortalité (p=0,001), avec IC (95%), [1,623-5,88].

Conclusion : En Tunisie, le pronostic de la cirrhose virale B après la première décompensation est mauvais puisque un malade sur 5 seulement a pu survivre au-delà de 5 ans. L'ascite représente la complication la plus fréquente. Un taux de gammaglobuline supérieur à 18g/l est un facteur indépendant prédictif de mortalité.

Mots-clés

Hépatite chronique B, Cirrhose, Décompensation, Survie

SUMMARY

Aim: To define the natural long term course of viral B cirrhosis after the onset of hepatic decompensation and to determine the predictive factors of death.

Methods: Retrospective longitudinal study including 77 cases of viral B cirrhosis among 192 consecutive patients with cirrhosis, hospitalized between 1997 and 2005 for the first hepatic decompensation. All those patients were followed- up until death or until December 2006. The probability of survival after the first hepatic decompensation was calculated using the Kaplan Meier method. The predictive factors of death were determined through univariate and multivariate analyses with the Cox regression model.

Results: Fifty four men and 23 women with an average age of 54±14.9 years were hospitalized for the first decompensation of the viral B cirrhosis. The 77 patients had been under observation for an average period of 24.2 ±21.1 months. During that time 64% among them died. The probability of survival after decompensation was 47% in 2 years and 22 % in 5 years. During follow- up, ascites was the most frequent decompensation (85%) followed by hepatic encephalopathy (38 %), variceal hemorrhage (34 %), jaundice (30%), hepato renal syndrome (27%), hepatocellular carcinoma (21%), and spontaneous bacterial peritonitis (14%). At univariate analysis four factors were predictive of death: Child Pugh C score (p=0.009), hepatocellular carcinoma (p=0.01), rate of serum gammaglobulin superior to18g / l (p=0.008) and prothrombin time inferior to 50 % (p=0.02). According to the multivariate analysis only the rate of serum gammaglobulin superior to 18g /l was an independent predictive factor of mortality (p=0,001) with IC (95 %) [1.623 - 5.88].

Conclusion: In Tunisia, the prognosis of viral B cirrhosis after the first decompensation is bad, because a patient on 5 only was able to survive beyond 5 years. Ascites is the most frequent decompensation. Only the rate of serum gammaglobulin superior to 18g / l is an independent predictive factor of mortality.

Key-words

Chronic hepatitis B, Cirrhosis, Decompensation, Survival

Chronic hepatitis B (CHB) virus infection is a major health problem that affects more than 300 million people worldwide (1). It is the most important cause of cirrhosis, and hepatocellular carcinoma (HCC) in the Far East. In hepatitis B virus (HBV) infected patients, the annual incidence of cirrhosis development is between 1.3% and 2.4 % (2). The hepatic decompensation also occurs at an annual rate of 2.3% among the patients (3). Although it is known that the prognosis worsens significantly after the onset of hepatic decompensation, the natural history of this very late stage of the HBV cirrhosis is not yet well understood because previous studies on patients with decompensated liver disease have predominantly recruited those with alcohol-related liver disease. A clear understanding of the natural history of the HBV cirrhosis patient after the onset of hepatic decompensation is essential for a better clinical management. In particular, patients with poor prognosis should be listed for orthotopic liver transplantation. The aim of the current study is to define the natural long term course of cirrhosis viral B after the onset of hepatic decompensation and determine the predictive factors of death.

PATIENTS AND METHODES

Study population

This is a retrospective longitudinal study included all patients with HBV cirrhosis hospitalized between 1997 and 2005 for the first decompensation in the Hepato- Gastroenterology department in Sahloul hospital, Sousse. Diagnosis of cirrhosis was based on clinical, biological and morphological criteria. Viral B origin was defined by the presence of antigen HBs and/or anti HBc antibody. Hepatic decompensation was defined as the presence of one or more of the following: jaundice, ascites, hepato-cellular carcinoma (HCC), infection, hepatic encephalopathy (HE), or variceal hemorrhage. The diagnosis of HCC was made based on high alpha-fetoprotein values (>400 ng/mL) and compatible ultrasonic findings. Diagnostic with HE was established in the presence of mental confusion, disorientation, abnormal behavior etc. Variceal hemorrhage was confirmed by endoscopic examination in the presence of oesophageal or gastric varices.

Sixty seven patients (44 men and 23 women) among 192 cirrhotic with HBV cirrhosis who had clearly documented first episodes of decompensation were included in the cohort.

The exclusion criteria were non B viral cirrhosis, patients with other co-factors able to deteriorate the liver function (virus C, alcohol consumption, hemochromatosis, auto-immune hepatitis or primary biliary cirrhosis), and patients with severe concomitant diseases (respiratory failure, cardiac failure, or concurrent malignancy (except hepato-cellular carcinoma).

Follow up

All patients had a regular follow-up lasting from 3 to 6 months (or more frequently, as clinically indicated). The routine evaluation of the patient included clinical assessment, standard liver biochemical tests, alpha-fetoprotein, and ultrasonic examination. All patients were followed- up until death or until December 2006. Medical files were elaborated including the date, the type of first hepatic decompensation, the clinical signs, and the biological parameters as early as at the first hepatic decompensation, the number and type of the major complications of cirrhosis during the follow up, the causes of mortality for every patient. Major complications of liver disease after the onset of hepatic decompensation were grouped as: jaundice, ascites, HCC, HE, hepatorenal syndrome, variceal hemorrhage and spontaneous bacterial peritonitis.

Hepatorenal syndrome was established in the presence of decreased urine output, serum creatinine level > 1.5 mg/dl, no sustained improvement in renal function after diuretic withdrawal and expansion of plasma volume with 1.5 l of plasma expander and absence of shock, ongoing bacterial infection and fluid losses.

Spontaneous bacterial peritonitis was diagnosed in the presence of monomicrobial infection of ascites and or polymorphonuclear count >250 cell/ mm^3 associated or not with symptoms.

Data Analysis

The probability of survival after the onset of hepatic decompensation was calculated using the Kaplan Meier method 7(4). Twenty variables were collected during the first decompensation for analysis. The predictive factors of death were determined through univariate and multivariate analyses with Cox regression model (5). The statistical significance was taken as $p < 0.05$. The analyses were performed using the SPSS 9.0 package (SPSS Inc., Chicago, IL, U.S.A.).

RESULTS

General patient's characteristics

Fifty four men and 23 women with an average age of 54±14,9 years were hospitalized for the first decompensation B viral cirrhosis. Most patients originate from Sousse (29%), Kairouan (26%), Mahdia (9%) and Sidi Bouzid (16%). Physical examination in these patients showed a splenomegaly in 50% of the cases, a hepatomegaly in 13% of the cases and jaundice in 30% of the cases. The blood count showed anemia in 50% of the cases, thrombopenia in 53% of the cases, a leucopenia in 27% of the cases. Hepatic exploration showed an average prothombin index of 53%, it was less than 50% in 44% of the cases; the alkaline phosphatase was elevated in the 22% of cases, gamma glutamyl transpeptidase (GGT) in 36% of the cases and transaminase in 46% of the cases. The albuminemia was inferior to 30g/l in 48% of the cases.The cirrhosis was classified as Child Pugh A in 25%, B in 50% and C in 25% of the cases. The endoscopic examination showed esophageal grade 1 varices in 15% of the cases, grade 2 in 41% of the cases and grade 3 in 18% of the cases. None of those patients received an antiviral treatment and benefit from a liver transplant.

Initial complications and during follow-up

Ascites was the most frequent first decompensation (66%), followed by jaundice (30%), variceal hemorrhage (23%), HCC (15 %), HE (9 %) and spontaneous bacterial peritonitis (5 %). During the average follow up of 24,2 ±21,1months (range 1-108 months) 85 % of the patient had ascites, 38% had HE, 34% had

variceal hemorrhage, 30% had jaundice , 27 % developed hepatorenal syndrome , 21% had HCC and 14% had spontaneous bacterial peritonitis (Table 1).

Table 1 : Complications at inclusion and during follow-up

	Initials complications (%)	Complications during follow-up (%)
Ascites	66	85
Jaundice	30	30
Variceal hemorrhage	23	34
Hepatocellular carcinoma	15	21
Spontaneous bacterial peritonitis	5	14
Hepatic encephalopathy	9	38
Hepatorenal syndrome	0	27

Survival and the predictive factors of death

During a follow up of 24 months, 64% of patients died. The global survival of our patients was 47% in 2 years and 22 % in 5 years. The causes of death were multiple and sometimes associated. It was HCC in 13 cases (17%), hepato renal syndrome in 18 cases (23%), HE in 17 cases (17%), spontaneous bacterial peritonitis in 3 cases and gastrointestinal bleeding in 3 cases (Table 2).

Table 2 : Causes of death

	Number of cases	Percentage
Cause of death	13	17
Hepatocellular carcinoma	18	23
Hepatorenal syndrome	17	22
Hepatic encephalopathy	3	4
Spontaneous bacterial peritonitis	3	4
Variceal hemorrhage		

The univariate analysis revealed four factors predictive of death: Child Pugh C score (p=0,009), the HCC (p=0,01), serum gammaglobulin superior to 18g / l (p=0,008) and prothrombine index inferior to 50 % (p=0,02) (Table 3). In the multivariate analysis only the serum gammaglobulin superior to 18g / l was an independent predictive factor of mortality (p=0,001) with IC (95 %) [1,623 -5, 88] (Table 4).

Table 4 : Predictive factors of death at multivariate analysis

Variables	P	OR	IC
Child Pugh score >9	0.19	1.654	(0.77-3.53)
HCC	0.3	1.398	(0.73-2.65)
Gammaglobulin >18g/l	0.001	3.09	(1.62-5.88)
Prothrombin time <50%	0.65	1.172	(0.58-2.35)

DISCUSSION

The first decompensation of viral B cirrhosis is observed relatively in young people whose ages range between 45 and 54 years (3, 6). Male gender is predominant in HBV cirrhosis (86%-95%) (5,7). Previous cross-sectional studies have shown that the male-to-female ratio increased proportionally during the course of chronic HBV infection: the ratio was 1-2/1 in the immune-tolerant phase (HBe Ag-positive patients with normal aminotransferase), 5–6/1 in chronic hepatitis, and 6–8/1 in cirrhosis (8). These data suggest that male HBs Ag carriers are more likely to have progressive liver disease than carriers of female gender and may explain the predominance of male gender in HBV cirrhosis. It was estimated that the annual rate of hepatic decompensation was 4% in patients with replicative cirrhosis and 1% in those with non replicative cirrhosis (9).

In the first decompensation of the HBV cirrhosis displayed in our series and in that of Yui Hui (6), ascites represented initial complication more frequently observed up to 2/ 3 patients, followed by jaundice and variceal hemorrhage.

In viral B and D cirrhosis (10) ascites was also the first and the more frequent complication (81 %) followed by jaundice (31 %), gastrointestinal bleeding (29 %), HCC and HE (each 12 %). In our study HCC and HE were respectively present with the rates of 15 and 9 %. Contrary to the viral C cirrhosis, Benvegnu and al (11) showed that HCC was the first complication to be observed (19 %), followed by ascites (10 %).

In our study, during the follow-up, we noticed that the prevalence of jaundice remained stable, whereas the prevalence of ascites, bleeding, hepatic encephalopathy, hepato renal syndrome, hepatocellular carcinoma and spontaneous bacterial peritonitis increased (table 1).

The 5-year survival rate of compensated HBV cirrhosis did not vary much in most reported series, and ranged from 80 to 85 % (3, 7, 9, 12). As the hepatic decompensation developed, the 5-year survival rate decreased considerably in most reported series (6, 7, 9, 13, 14, 15). The survival rate of decompensated cirrhosis varies considerably in different series, possibly because of the difference in the inclusion criteria among different studies. The study of De Jongh and al (7) which included a smaller number of patients (n =21) showed one rate of survival equal to 45 % in 2 years and to 14 % in 5 years.

Even in larger series that studied survival from the onset of the first major decompensation, survival rates varied remarkably as well: the 2-year survival rate was 80% in one study from Hong Kong (6) and only 45% in two studies from Europe (9, 16). In our series, the rate of survival was 47 % in 2 years and 22 % in 5 years.

Only two studies (6, 10) determined the predictive factors of death in viral B, and B-D cirrhosis after the onset of hepatic decompensation. The first study showed that hepatic encephalopathy and hypo albuminemia (<2.8 g/dL) were predictive of poor survival in 2 years. The second study has shown that the presence of gastrointestinal bleeding negatively predicted the risk of death, wile the Model of End –Stage Liver

Table 3 : Predictive factors of death at univariate analysis

Variables	Number of patients	Survival at 2 years (%)	Survival at 5 years (%)	Median survival	P
SEXE :Men	54	46.5	12.1	21	
Women	23	50	40	24	0.08
Jaundice					
Present	30	38.8	14.8	10	
Absent	47	55.2	29.5	35	0.07
Ascites					
Present	51	53.8	24.9	27	
Absent	26	65.8	54.8	39	0.11
variceal hemorrhage					
Present	18	62.8	35.9	35	0.84
Absent	57	51.9	31.9	28	
HE					
Present	7	57.3	31.2	30	0.52
Absent	70	66.7	35	28	
HCC					
Present	12	25	0	13	0.01
Absent	65	67.8	43	57	
Prothrombin index (%)					
>50	42	71.6	48.5	13	0.02
<50	35	41.6	23.1	31	
Alkaline phosphatase					0.21
Normal	60	62	32.6	38	
Increased	17	40	30	6	
GGT					0.7
Normal	42	83.3	67.3	18	
Increased	35	36.7	9.6	22	
Platelets					0.98
<75000/mm^3	34	68	27.7	8	
>75000/mm^3	43	52.4	42.3	27	
Child Pugh score					0.009
<9	57	74.3	38.7	57	
>9	29	23.5	17.6	8	
Gammaglobulin					0.008
<18 g/l	36	83.3	67.3	72.4	
>18 g/l	41	36.7	9.6	18	
Serum albumin					0.6
<30 g/l	37	50	32.8	21	
>30 g/l	40	82.3	41.5	57	

Disease score higher than 15 was positively associated with death in patients with viral B and D cirrhosis. In our study only the rate of gammaglobulin superior to 18g / l was an independent predictive factor of mortality. The study of Gines and al (17) including 293 patients with cirrhosis (alcoholic origin 42 %, viral B origin 8 %) showed that hyper gammaglobulinemia was also one predictive factor of bad prognosis. Hyper gammaglobulinemia in cirrhosis is considered to be the consequence of an increased antibody production caused by the passage of the intestinal antigen into the general circulation (18, 19). This phenomenon is due to the impaired hepatic reticulo- endothelial system phagocytic activity (18, 19). Other studies indicate that this abnormality is related to the intrahepatic shunting of blood (20, 21). Rimola et al (22) have reported that the reticulo- endothelial system phagocytic activity, estimated by the plasma disappearance rate of 99m technetium- sulfur colloid, has also prognostic in the decompensated cirrhosis.

In recent publications and in our study, HCC and the complications of the liver failure are the main causes of mortality for the patients with cirrhosis (10, 11, 23). The gastrointestinal bleeding has become a rare cause of mortality

(3 in 6 %) thanks to the development of pharmacological and endoscopic treatment (10, 24).In our series, only three patients died of gastrointestinal bleeding.

Our work has the limitations associated with a retrospective study.We did not routinely test all the CHB patients with hepatitis D virus and the replicative status of HBV (HBe Ag, HBV DNA titer).

Chung et al (14) have shown that survival was significantly greater in those patients without serum HBe Ag at presentation than in those with serum HBe Ag.

The lamivudine therapy is associated with the rapid viral suppression and the improved Child-Pugh score (25, 26). Nevertheless, the prolonged use of lamivudine increases the risk of appearance of YMDD mutants and so reduces the efficiency of this treatment (27).

Adefovir or entecavir is preferred for the patients with decompensated cirrhosis who require a long duration of treatment, due to the lower rate of development of resistance (28).In our study no patient has had an antiviral treatment.

CONCLUSION

In Tunisia, the prognosis of HBV cirrhosis after the first decompensation is poor. The probability of survival is 22 % in 5 years. Hepatic failure and HCC are the two main causes of death. Only the rate of gammaglobulin superior to 18g / l is independent predictive factor of mortality

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