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• VIRAL HEPATITIS •

Early diagnosis of bacterial and fungal infection in chronic cholestatic hepatitis B

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Abstract

AIM: To investigate the early diagnostic methods of bacterial and fungal infection in patients with chronic cholestatic hepatitis B.

METHODS: One hundred and one adult in-patients with chronic hepatitis B were studied and divided into 3 groups: direct bilirubin (DBil)/total bilirubin (TBil) 0.5, without bacterial and fungal infection (group A, *n*=38); DBil/TBil <0.5, without bacterial and fungal infection (group B, *n*=23); DBil/TBil 0.5, with bacterial or fungal infection (group C, *n*=40). The serum biochemical index and pulse rate were analyzed.

RESULTS: Level of TBil, DBil, alkaline phosphatase (ALP) and DBil/ALP in group A increased compared with that in group B. The level of ALP in group C decreased compared with that in group A, whereas the level of TBil, DBil and DBil/ALP increased (ALP: 156±43, 199±68, respectively, *P*<0.05; TBil: 370±227, 220±206, respectively, *P*<0.01; DBil: 214±143, 146±136, respectively, *P*<0.01; DBil/ALP: 1.65±1.05, 0.78±0.70, respectively, *P*<0.001). The level of DBil and infection affected DBil/ALP. Independent of the effect of DBil, infection caused DBil/ALP to rise (*P*<0.05). The pulse rate in group A decreased compared with that in group B (63.7±6.4, 77.7±11.4, respectively, *P*<0.001), and the pulse rate in group C increased compared with that in group A (81.2±12.2, 63.7±6.4, respectively, *P*<0.001). The equation (infection=0.218 pusle rate +1.064 DBil/ALP -16.361), with total accuracy of 85.5%, was obtained from stepwise logistic regression. Pulse rate (80/min) and DBil/ALP (1.0) were used to screen infection. The sensitivity was 62.5% and 64.7% respectively, and the specificity was 100% and 82.8% respectively.

CONCLUSION: Bacterial and fungal infection deteriorate jaundice and increase pulse rate, decrease serum ALP and increase DBil/ALP. Pulse rate, DBil/ALP and the equation (infection=0.218 pusle rate+1.064 DBil/ALP-16.361) are helpful to early diagnosis of bacterial and fungal infection in patients with chronic cholestatic hepatitis B.

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INTRODUCTION

Patients with chronic hepatitis are known to be abnormally susceptible to infection as a result of multiple immunologic defects[1-6]. The incidence of bacteriemia in chronic liver disease is 5- to 7- fold higher than that found in other hospitalized patients[7]. Infection is often associated with systemic inflammatory response syndrome and multiple organ dysfunction syndrome that is easy to develop into liver failure[8,9]. Infection can prove fatal either directly or by precipitation of encephalopathy, gastrointestinal hemorrhage, hepatic hemodynamic derangement, portal hypertension, or renal failure[9-17]. About 33% mortality in bacteriemic patients with chronic liver disease has been noted[18]. Considering the low positivity rate and lengthy bacterial culture, severe chronic liver disease patients with clinical diagnosis of infection should get the antibiotic treatment immediately to improve the survival opportunity before pathogen diagnosis[19-24]. However, clinical diagnosis is made more difficult by the absence of the typical clinical feature of infection - that is, fever, leucocytosis, and localized symptoms[9, 21]. Clinically apparent focus of infection could not be found in 20% to 60% of bacteriemic patients with chronic liver disease[9, 25, 26]. No specific site is identified in one third to one half of the infections, in which case the only clue may be deterioration of hepatic precoma or coma or renal function. The preventive antibiotic treatment is often applied to serious patients who have the liability to infection (such as the protein in ascites <10 g/L, gastrointestinal hemorrhage, and previous spontaneous bacterial peritonitis), and in the meantime it might increase the risk of drug resistance[19, 27-30]. The early diagnostic methods of secondary bacterial and fungal infection in patients with chronic hepatitis B have not been studied. To reduce infection related mortality, the development of new methods for early diagnosis is of great significance.

MATERIALS AND METHODS

Patients

One hundred and one adult in-patients with chronic icteric hepatitis B in West China Hospital from October 2002 to March 2003 were studied and divided into three groups: direct bilirubin (DBil)/total bilirubin (TBil) 0.5, without bacterial or fungal infection (group A, *n*=38); DBil/TBil <0.5, without bacterial or fungal infection (group B, *n*=23); DBil/TBil 0.5, with bacterial and fungal infection (group C, *n*=40).

Inclusion criteria

All patients in the study met with the following criteria: positive HBsAg or HBVDNA; TBil >17.1 mmol/L; age between 14 to 65 years. In addition, the patients in group C had the following features: leukocytes 10×10^9/L or neutrophils 7×10^9/L or the ratio of neutrophil 70 % in blood; leukocytes in urine 5 per visual field under high power microscope; leukocytes 0.5×10^9/L or neutrophils 0.25×10^9/L in ascites; bacterial culture of blood, urine, phlegm or ascites was positive.

Exclusion criteria

The patient who had one of the followings was excluded from

group A and group B: infected with other pathogens rather than HBV; complicated with other diseases which had not relation with hepatitis B; recently occurring gastrointestinal hemorrhage. The patient who had one of the followings was excluded from group C: infected with other virus; complicated with other liver diseases which had not relation with hepatitis B; recently occurring gastrointestinal hemorrhage; leukocytes in urine 5 per visual field under high power microscope but normal in routine blood test in female patients who were in menstruation or in patient who had non-inflammatory nephrosis.

Investigation indexes

Blind tests for TBil, DBil, indirect bilirubin (IBil), DBil/IBil, alanine aminotransferase (ALT), aspartate aminotransferase (AST), AST/ALT, serum total protein (TP), albumin (ALB), globulin (GLOB), ALB/GLOB, γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), DBil/ALP, lactate dehydrogenase (LDH), cholinesterase (ChE), serum total bile acid (TBA) and pulse rate were performed. The first liver biochemical test of group A and B after hospitalization and the first liver biochemical test of group C after confirmation of infection were done, and pulse rate of all patients were measured after 15-min bed rest.

Statistical analysis

All data were presented as mean±SE. Analysis of variance and covariance was used to determine whether there were significant differences among the three groups. Data with significant difference were entered into a stepwise logistic regression analysis. Statistical calculations were performed by SPSS (Version: 11.0, Chicago, USA).

RESULTS

Clinical features of infection

Fifteen percent of patients in group C showed a rise in leukocyte or neutrophil in blood, 55% of patients showed a rise in the ratio of neutrophil in blood lightly, and 12.5% of patients showed an increase in leukocyte or neutrophil in ascites. Eleven patients showed a leukocyte rise in urine (in these cases, 5 patients showed an increase in leukocyte or neutrophil in blood or in the ratio of neutrophil, 5 patients had a history of fever, 2 patients showed spontaneous bacterial peritonitis). Fifteen patients presented with the localized symptoms of infection. Sixteen patients had a history of fever (the fever was light and persisted shortly in most patients). Positivity rate of bacterial culture was 25% (3/12).

Table 1 Comparison of serum bilirubin

Group	Case	Tbil (μmol/L)	DBil (μmol/L)	IBil (μmol/L)	DBil/TBil
A	38	220±206	146±136	73±72	0.660±0.078
B	23	59±33[b]	22±12[d]	38±23	0.361±0.105[d]
C	40	370±227[bf]	214±143[bf]	136±92[df]	0.631±0.840[f]

[b]P<0.01 *vs* group A; [d]P<0.001 *vs* group A; [f]P<0.001 *vs* group B.

Analysis of variance

Level of TBil, DBil, ALP and DBil/ALP in group A increased significantly compared with that in group B (P<0.01, P<0.01, P<0.05, P<0.01, respectively). The level of ALP in group C decreased compared with that in group A (156±43, 199±68, respectively, P<0.05), whereas the level of TBil, DBil and DBil/ALP increased significantly (TBil: 370±227, 220±206, respectively, P<0.01; DBil: 214±143, 146±136, respectively, P<0.01; DBil/ALP: 1.65±1.05, 0.78±0.70, respectively, P<0.001). The level of IBil in group C decreased compared with that in group A (P<0.001) (Tables 1, 2).

The pulse rate in group A decreased significantly compared with that in group B (63.7±6.4, 77.7±11.4, P<0.001). The pulse rate in group C increased compared with that in group A and normal adults (81.2±12.2, 63.7±6.4, 72, P<0.001), but decreased compared with that in infectious patients without hepatitis (81.2±12.2, 90, P<0.001) (Table 2, Figure 1).

The level of ALT, AST, AST/ALT, TP, ALB, GLOB, ALB/GLOB, GGT, LDH, and ChE showed no significant difference among the three groups (data not shown).

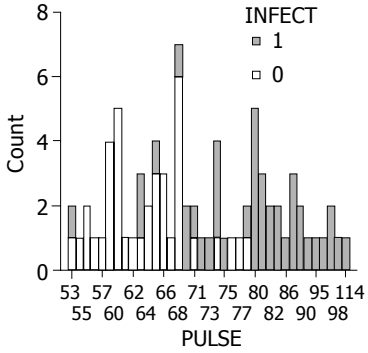

Figure 1 Pulse rate in cholestatic patients. 1: With bacterial or fungal infection; 0: Without bacterial and fungal infection.

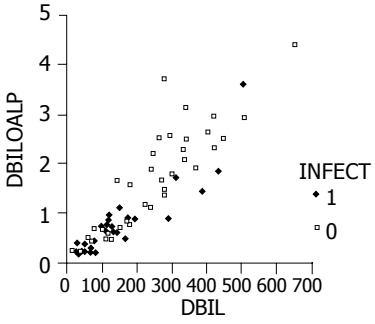

Figure 2 DBil/ALP and DBil in cholestatic patients. 1: With bacterial or fungal infection, 0: Without bacterial and fungal infection.

Analysis of covariance

There was linear correlation between DBil and DBil/ALP in groups A and C, and the distribution of DBil between the two groups was closely similar (Figure 2). The level of DBil and infection affected DBil/ALP (P<0.05, P<0.001, respectively)

Table 2 Comparison of TBA, ALP, DBil/ ALP and pulse rate (mean±SE)

Group	*n*	TBA(μmol/L)	*n*	ALP(U/L)	*n*	DBil/ALP	*n*	Pulse rate(times/min)
A	22	148±89	29	199±68	29	0.78±0.70	38	63.7±6.4
B	16	31±17[d]	18	149±50[a]	18	0.14±0.06[b]	23	78±11[d]
C	22	140±60[f]	34	156±43[ac]	34	1.65±1.05[df]	40	81±12[d]

[a]P<0.05 *vs* group A; [c]P<0.05 *vs* group B; [b]P<0.01 *vs* group A; [d]P<0.001 *vs* group A; [f]P<0.001 *vs* group B.

(Table 3). Independent of the effect of DBil, infection caused DBil/ALP to rise (P<0.05) (Table 4).

Table 3 Tests of between-subjects effects (dependent variable: DBil/ALP)

Source	Type III sum of squares	Df	Mean square	F	P
Corrected model	50.025	2	25.012	129.672	<0.001
Infection	1.172	1	1.172	6.074	0.017
DBil	38.709	1	38.709	200.682	<0.001

Table 4 Pairwise comparisons (dependent variable: DBil/ALP)

Infection I	Infection J	Mean difference(I-J)	SE	P	95%	CI
1	2	-0.293[1]	0.119	0.017	-0.531	-0.055
2	1	0.293[1]	0.119	0.017	0.0551	0.531

[1]The mean difference is significant at the 0.05 level.

Logistic regression

The stepwise logistic regression was used to establish the best statistical model to early diagnose infection, and the equation (infection=0.218 pulse rate+1.064 DBil/ALP -16.361, P<0.001) was obtained. Its overall accuracy was 85.5%, and accuracy for diagnosing infection and noninfection were 85.7% and 85.3%, respectively (Table 5).

Table 5 Logistic analysis of bacterial and fungal infection

	B	SE	Wald	Df	P	Exp (B)
Pulse rate	0.218	0.059	13.468	1	<0.001	1.244
DBil/ALP	1.064	0.447	5.657	1	0.017	2.899
Constant	-16.361	4.251	14.815	1	<0.001	<0.001

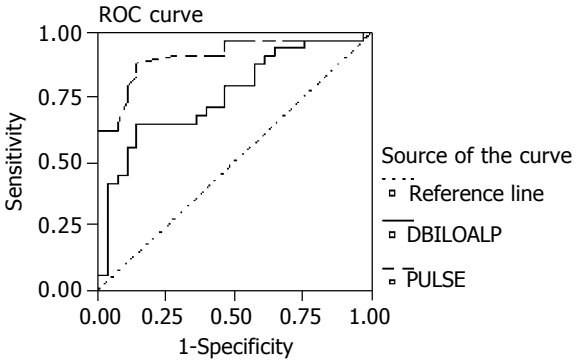

Figure 3 Receiver operator characteristic curve of pulse rate and DBil/ALP.

Screening test

Because the diagnostic index of pulse rate at 80/min to screen infection was the greatest, the cut off point was selected at 80/min (Figure 3). The sensitivity (Sen), specificity (Spe), diagnostic index (DI), false positive rate (α), false negative rate (β), Youden's index (γ), crude accuracy (CA), adjusted agreement (AA), positive predictive value (PV+) and negative predictive value (PV-) were 62.5%, 100%, 1.625, 100%, 71.7%, 62.5%, 80.8%, 83.6%, 0% and 37.5%, respectively. Area under the curve (Az)=0.889 (P<0.001) (Table 6). Because the diagnostic index of DBil/ALP at 1.0 was the greatest, the cut off point was selected at 1.0 (Figure 3). Sen, Spe, DI, α, β, γ, CA, AA, PV+ and PV- were 64.7%, 82.8%, 1.475, 81.5%, 66.7%, 47.5%, 73.0%, 73.9%, 17.8% and 35.3%, respectively. Az=0.7373 (P<0.001) (Table 6). Pulse rate was a better index than DBil/ALP (P<0.001).

DISCUSSION

Bacterial and fungal infections are the common complications of chronic hepatitis, frequently aggravating hepatitis. Since the bacterium culture in chronic hepatitis patients is often negative, clinical diagnosis plays a major role. However, a large number of patients do not often present with the typical clinical features of infection. In a prospective study, fever was initially absent in 45% of cases, and leukocytosis was absent in 25% of cases[10]. Urinary tract infection is the common type of infection and the source of bacteriemia in up to 50% of patients with cirrhosis, and 20% of episodes of spontaneous bacterial peritonitis[10-30]. However, patients with urinary tract infection often do not have localized symptoms or physical findings[10,1]. Careful urinalysis is important to exclude infection in patients with chronic liver disease[10]. In our study, the leukocyte or neutrophil in blood rose in 15% of infected patients, and the ratio of neutrophil rose lightly in 55% of patients. Leukocyte or neutrophil in ascites increased in 5 patients, and leukocyte in urine rose in 11 patients. Sixteen patients had a history of fever (the fever was mild and short-lasting in most patients). Only 37.5% of patients presented localized symptoms of infection. The positivity rate of bacterial culture was 25%(3/12). Therefore, early diagnosis of bacterial and fungal infection is difficult in chronic hepatitis.

The level of ALP frequently rises in cholestatic patients. However, in serious liver disease, along with the increase of serum TBil and DBil, sometimes ALP decreased. Hadjis discovered that the synthesis of ALP decreased in the case of widespread hepatocyte necrosis. As well as ALT and AST, it is a marker of disease aggravation. In our study, the level of TBil and DBil in cholestatic patients with infection increased compared with that without infection, but ALP in infection patients decreased compared with that without infection.

In order to characterize the contrary alteration of DBil and ALP in infection patients, we introduced a new index -that is the ratio of DBil to ALP. The level of DBil/ALP showed significant difference between the three groups (0.7829±0.7002, 0.1377±0.0652, 1.6468±1.0500, respectively, P<0.01). Analysis of covariance showed that the level of DBil and infection affected DBil/ALP, and independent of the effect of DBil, infection led to DBil/ALP increase (P<0.05).

To test whether DBil/ALP could be used to screen infection, a screening test was performed. Its sensitivity, specificity, positive predictive value and negative predictive value were 64.7%, 82.8%, 81.5% and 66.7%, respectively (the cut off point at 1.0). Therefore, we hypothesize that DBil/ALP can be used as an "infection index" to diagnose infection early in chronic cholestatic hepatitis B. If DBil/ALP is greater than 1.0, the probability of infection is 82.8%.

The mean pulse rate in normal adults is 72/min, but it frequently increases in infection, often above 90/min. Because the vagus's excitement increased in cholestatic patient, the

Table 6 Screening test of bacterial and fungal infection

Diagnosis		Sensitivity	Specificity	Diagnostic Index	A_Z	Z	P
Pulse rat	80/min	0.625	1.000	1.625	0.889	20.372	<0.001
DBil/ALP	1.0	0.647	0.828	1.475	0.7373	4.022	<0.001

pulse rate decreased compared with that in normal adults (63.7±6.4, 72, $P<0.001$). Although the pulse rate in cholestatic patient increased after infection (81.2±12.2, 63.7±6.4, $P<0.001$), it was slower compared with that in infection patients without cholestasis (81.2±12.2, 90, $P<0.001$). That is why alteration of pulse rate in those patients is likely to be neglected in clinic.

To test whether pulse rate could be used to screen infection, a screening test was done. Its sensitivity, specificity, positive predictive value and negative predictive value were 62.5%, 100%, 100% and 71.7%, respectively (the cut off point at 80/min). Pulse rate was better for screening infection than DBil/ALP ($P<0.001$).

In order to establish the best statistical model to diagnose infection early, the equation (infection=0.218 pulse rate+1.064 DBil/ALP - 16.361, $P<0.001$) was obtained from the stepwise logistic regression. Its total accuracy, the accuracy of diagnosing infection and noninfection was 85.5%, 85.7% and 85.3%, respectively.

It is interesting that there is notable relationship between the logistic equation and screening test. Among the 18 indexes that we studied, only pulse rate and DBil/ALP could affect the logistic equation. The equation can be described approximately as "infection 0.2 pulse rate + DBil/ALP – 16". As 0.2 multiplied by 80 is 16, if pulse rate 80/min, the equation 0 obviously. But if pulse rate <80/min, DBil/ ALP significantly affects the equation. For severe chronic cholestatic hepatitis B, if pulse rate 80/min, perhaps the antibiotic treatment should be applied immediately before pathogen diagnosis to improve the survival opportunity. If DBil/ALP 1.0 but pulse rate <80/min, the equation is helpful to estimate the probability of infection. If DBil/ALP < 1.0 and pulse rate <80/min, the equation is useful to exclude infection. It is a sensitive, quick, simple and economical method to diagnose infection early and possibly improve the survival opportunity of severe chronic cholestatic hepatitis B.

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