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The predictive value of admission and follow up factor V and VII levels in patients with acute hepatitis and coagulopathy

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***Background/Aims*: Low factor V and VII levels are bad prognostic indicators in fulminant hepatic failure (FHF). The prognostic importance of admission versus follow up levels of these factors in patients with acute hepatitis and coagulopathy without encephalopathy has not been evaluated.**

***Methods*: Clinical and laboratory data from 68 consecutive patients with acute hepatitis and coagulopathy but without encephalopathy, during a 6-year period, was retrospectively evaluated.**

***Results*: Sixty patients (88%) demonstrated improvement in liver function and coagulation ('survivors'), while 8 patients (12%) died or underwent OLT ('non-survivors'). Survivors had higher admission ($P<0.005$) and follow up factor VII levels ($P<0.005$) than non-survivors. Follow up factor V levels were higher in survivors ($P<0.02$), while admission factor V level was not different between groups ($P=$NS). Multivariate logistic regression analysis demonstrated that admission factor VII levels predicted outcome ($P<0.006$). Area under the ROC curve of factor VII was larger than that of factor V (0.885 and 0.715, respectively, $P<0.02$). After 3 days of hospitalization, factor V levels, but not factor VII, independently predicted outcome ($P<0.04$).**

***Conclusions*: In patients with hepatitis and coagulopathy without encephalopathy at presentation, admission factor VII level may serve as a reliable prognostic marker. Subsequently, during hospitalization, changes in factor V are better outcome indicators.**

***Keywords*: Hepatitis; Coagulation; Factor VII; Factor V**

1. Introduction

Acute hepatic failure is often associated with a wide spectrum of coagulation abnormalities, mainly due to reduced hepatic production and increased peripheral consumption of coagulation factors [1]. Prolongation of prothrombin time is associated with poor outcome in patients with acute liver failure [2]. Due to their relatively short half-lives, factors V and VII are commonly used in prognostic evaluation in this setting [3–6].

Many patients, presenting with acute hepatitis that is associated with coagulopathy, do not fulfill other criteria for acute liver failure at presentation. Many of these patients develop prolonged prothrombin time and reduced levels of factor V and VII, but fully recuperate and regain normal hepatic synthetic function shortly afterwards. Only a minority of these patients feature worsening hepatic function and develop life-threatening fulminant hepatic failure. Early identification of this small subgroup of patients is crucial, since early referral to liver transplantation centers is needed.

The associations between admission and follow up levels of factors V and VII in patients without fulminant hepatic

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Abbreviations PTT, partial prothrombin time; PT, prothrombin time; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

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failure has not been widely reported [7]. In our study, 68 consecutive cases of patients with hepatitis and coagulopathy were retrospectively evaluated, and the correlation between factor V and VII levels at admission and during follow up hospitalization and the subsequent outcome were assessed.

2. Methods

2.1. Patients

We reviewed the records of all patients who were admitted to Hadassah-Hebrew University Medical centers, Jerusalem, Israel between the years 1998 and 2003. The participating hospitals serve as primary, secondary and tertiary medical care facilities and perform liver transplantation. Included were patients who presented with liver enzyme elevation compatible with acute liver injury that was associated with a significant new-onset prolongation of prothrombin time (PT), defined as an INR level of greater than 1.7. Excluded were patients that fulfilled criteria for acute liver failure at presentation (including encephalopathy of any grade, hepatorenal syndrome, or multiorgan failure), those patients were divided into two groups according to outcome, to those who featured resolution of acute liver injury with normalization of coagulation abnormalities ('survivors'), and those who either died or required urgent orthotopic liver transplantation ('non-survivors').

2.2. Clinical and mortality information

Information was recorded using the patients' medical charts, including patient clinical records. Data included age, sex and etiology of acute hepatitis. Information on mortality was obtained using patients' medical records, liver unit transplantation records, and death certificates.

2.3. Laboratory evaluation

Aminotransferase activity and bilirubin, creatinine, urea, albumin and prothrombin time (PT) were recorded using standard automated procedures (automated chemistry analyzer Kodak-Vitros 950, Rochester, NY, USA and the coagulation time analyzers Acl 200 and 1000). Levels were monitored daily from admission until resolution of hepatitis, death, or transplantation.

Factors V and VII were measured at presentation in all patients using the same plasma sample. Factor measurements were performed according to international guidelines [8]. Patients' plasma was added to factor-deficient plasma. Coagulation time was compared to that of control plasma mixed with factor deficient plasma. Results were expressed as percents of control. Factor V and VII levels were measured repeatedly throughout the hospitalization period as clinically indicated. All laboratory tests were made by the same laboratory, using the same kits.

2.4. Data analysis

Fisher exact test and ANOVA method were used for the detection of differences in age, sex and etiology of hepatitis between the survivor and non-survivor groups. Fisher exact test, Mann–Whitney test and ANOVA were used to evaluate other differences in clinical and laboratory parameters. Continuous variables are presented as mean $\pm$SD. All statistical tests were two-tailed, and a P-value lesser than 0.05 was considered significant. Prediction of outcome was assessed by multivariate logistic regression, including admission parameters that were found to be significantly associated with outcome in univariate analyses. Statistical analyses and ROC curves were generated by Analyse-it software for Microsoft Excel.

3. Results

3.1. Baseline characteristics of the study population

Sixty-eight patients were admitted with hepatitis that was associated with coagulation abnormalities at presentation. The duration between onset of disease and admission ranged between 1 and 7 days. The survivor group included 60 patients (88%) who featured complete resolution of acute hepatitis, all within 3 weeks of admission (range 10–21 days). The non-survivor group included 5 patients (7%) who underwent successful liver transplantation, and 3 patients (4%) who died of FHF complications (e.g. brain edema, multiorgan failure, and sepsis). Baseline characteristics of the two study groups are shown in Table 1. The demographic parameters were not significantly different between survivors and non-survivors.

3.2. Clinical and laboratory presentation

Etiology of hepatitis differed between survivors and non-survivors (Table 1); there was a higher proportion of subjects with a favorable etiology (i.e. acetaminophen overdose, hepatitis A and hepatitis B) in the survivor group (58% versus 13% in non-survivors, $P<0.04$). All 12 patients with acetaminophen overdose survived. Laboratory values at presentation are listed in Table 1. Serum creatinine, urea, albumin, aspartate aminotransferase activity (AST) and alanine aminotransferase activity (ALT) did not differ significantly between patient groups. In contrast, total bilirubin levels were significantly higher in non-survivors (335 ± 203 μmol/l) than among survivors (118 ± 132 μmol/l, $P<0.0001$).

Table 1
Demographic clinical and laboratory data of the study groups

	Survivors ($n=60$)	Non-survivors ($n=8$)	P value
Age (years)	32 ± 19	21 ± 13	NS
Female gender (%)	34 (57)	2 (25)	NS
Etiology of hepatitis (%)			
Paracetamol	10 (17)	0 (0)	NS
Other drug/toxin	6 (10)	0 (0)	NS
Autoimmune	7 (12)	2 (25)	NS
Hepatitis A	17 (28)	1 (12.5)	NS
Hepatitis B	8 (13)	0 (0)	NS
Non-A, non-B	2 (3)	2 (25)	NS
Miscellaneous	5 (8)	1 (12.5)	NS
Unknown	5 (8)	2 (25)	NS
Bilirubin (μmol/l)	118 ± 132	335 ± 203	0.0001
Creatinine (μmol/l)	99 ± 207	85 ± 79	NS
Urea (mmol/l)	4.6 ± 5.3	3.8 ± 4.2	NS
Albumin (g/dl)	3.5 ± 0.6	3.2 ± 0.5	NS
AST (u/l)	2564 ± 4279	2385 ± 3755	NS
ALT (u/l)	2428 ± 2782	1604 ± 1543	NS