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Von Willebrand Factor Levels – A Predictor of Severity of Cirrhosis

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Abstract

Background and Aims: Von Willebrand factor (vWF) a surrogate marker of endothelial dysfunction is increased in patients with cirrhosis but the clinical significance is unclear. Von willebrand factor Antigen (vWF-Ag) plays an important role in primary haemostasis and development of thrombotic vascular obliteration which is a possible mechanism leading to portal hypertension. In this study we evaluated the association of serum vWF-Ag antigen (Ag) level with the severity of cirrhosis (according to Child-Pugh classification), its correlation with patients having thrombosis and size of oesophageal varices in cirrhotics.

Methods: We included 107 cirrhotic patients (Male 69%, Mean Age 52+11) in the study. Diagnosis of cirrhosis was made on the basis of biopsy, clinical, laboratory and imaging parameters. vWF-Ag level was done using Von Willebrand Factor antigen 96-microwell test kit from Helena biosciences Europe. The stage of cirrhosis was defined with Child-Pugh classification and MELD score. Data were analysed by using Statistical Package for the Social Sciences (SPSS) 10.0 software program.

Results: We observed there was no statistically significant difference in the VWF Ag levels with the increas¬ing stages of cirrhosis according to Child-Pugh score and size of oesophageal varices. vWF-Ag levels were significantly higher in patients with venous thrombosis than without thrombosis (p value- 0.03).

Conclusion: Our study does not show any correlation of increase in Serum vWF-Ag levels in with increase severity of cirrhosis and development of oesophageal varices as shown in previous studies.

Introduction

Coagulation cascade in patients with cirrhosis is delicately balanced between deficiency of anti and procoagulant factors. Tripodi recently showed that cirrhosis presents with thrombocytopenia and decreased levels of both pro- and anticoagulants; notable exceptions are factor VIII and vWF which are increased [1].

Normal coagulation has classically been conceptualized as a Y-shaped pathway, with distinct "intrinsic" and "extrinsic" components initiated by factor XII or factor VIIa /tissue factor, respectively, and converging in a "common" pathway at the level of the FXa /FVa (prothrombinase) complex [2]. Coagulation cascade in patients with cirrhosis is delicately balanced between deficiency of anti and procoagulant factors. Each of the 3 phases; haemostasis, coagulation, and fibrinolysis is affected by liver disease, but the effects of laboratory abnormalities on overall haemostasis have only recently been assessed. Primary haemostasis, the formation of the platelet plug on an endothelial defect, is considered to be defective in patients with cirrhosis due to qualitative platelet dysfunction and thrombocytopenia. However, compensatory mechanisms exist to restore platelet-endothelial interactions toward normal in patients with cirrhosis. Plasma concentrations of von Willebrand factor (vWF), the endothelial-derived protein responsible for adhesion of platelets to endothelial cells, are increased in patients with liver disease, which increases the stickiness of platelets. In addition, plasma concentrations of ADAMTS-13, a liver-derived protease that cleaves vWF into smaller and less sticky multimers, are decreased in patients with liver disease, again resulting in a relative increase in platelet adhesion to the endothelium [3].

vWF is a surrogate marker of endothelial dysfunction, but the clinical significance is in cirrhosis unclear. vWF plays an important role in primary haemostasis and development of thrombotic vascular obliteration which is a possible mechanism leading to portal hypertension. Studies have shown that vWF is a mediator that increases endotoxemic medium like in cirrhosis and this is more pronounced with higher stages of cirrhosis [4]. Thrombocytopenia (unless very severe) is no longer considered a bleeding risk as platelets from cirrhosis display normal adhesiveness in a flowing system that is mainly supported by the increased levels of vWF[5]. Two studies, one done in hepatitis B is cirrhosis patients and another done on cirrhotic patients of all aetiologies showed that vWF is a non invasive predictor of portal hypertension and oesophageal varices. vWF-Ag levels correlate with liver function, Hepatic venous pressure gradient and independently predict clinical outcome respectively[6,7]. This study concluded that vWF level is a new, simple and non invasive predictor of clinically significant portal hypertension (CSPH)and it may become a valuable non invasive marker for the prediction of mortality in patients with liver cirrhosis in clinical practice. But the use of vWF levels is still not recommended as a non clinical predictor of mortality because of lack of adequate data.

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So to contribute to the data on significance of vWF levels in cirrhotics we conducted this study. We evaluated the association of serum vWF-Ag level with the severity of cirrhosis (according to Child-Pugh classification), its correlation with patients having thrombosis and size of oesophageal varices in cirrhotics of all aetiologies.

Materials and methods

Study design

Prospective longitudinal hospital based study. It included 107 patients of cirrhosis of liver attending liver clinic (inpatient & outpatient). We prospectively enrolled 107 consecutive patients attending liver clinics with cirrhosis of liver of all age groups; any child class and any aetiology. Serum vWF-Ag levels were done in these 107 cirrhotic patients attending liver clinics and 30 healthy controls. The stage of cirrhosis was defined with Child-Pugh classification. Varices were classified as small (<5mm) and large (>5mm). Data were analysed by using Statistical Package for the Social Sciences (SPSS) 10.0 software program.

Inclusion criteria

All the patients with Cirrhosis of liver

- Diagnosis of cirrhosis was based on clinical, biochemical, endoscopic and imaging findings. Patients with histological evidence of cirrhosis were also included.
- The diagnosis of alcoholic cirrhosis was made on the basis of history of any form of daily alcohol consumption of >80g/dl in men and > 40g/dl in women for 10yrs.
- History, clinical examination, complete blood count with platelet count, liver profile, renal profile, oesophago gastroduodenoscopy.

Methods and Instruments: vWF: Ag assay

Done using von Willebrand Factor Antigen 96 microwell test kit by Helena biosciences, Gatesway, Europe. Blood samples were collected with the double-syringe technique from a clean venipuncture at the antecubital fossa. Whole blood 3.5 mL was collected into a 5 ml syringe and in accordance with manufacturer recommendation, analyzed within 8 minutes from sampling using vWF-Ag 96-microwell test kit (Normal range was 47-197%).

Data was entered in excel sheet to prepare master chart and subjected for statistical analysis. Quantitative data was summarized as mean and standard deviation (SD), while nominal/categorical data was summarized as percentages. Unpaired' test & one way ANOVA test were used for comparison of quantitative data. Pearson Correlation coefficients & Spearman's rho correlation coefficient were calculated to assess correlation between numerical & ordinal variables respectively. P<0.05 was taken as significant. MedCalc 12.2.1.0 version software was used for all statistical calculations.

All patients provided a written informed consent. The study protocol was approved by the institutional ethics committee namely Bombay hospital ethics committee (Ethics committee registration number – ECR/296/Inst/MH/2013). Funding of the study is done by Rameshwar Birla Smarak kosh.

Results

vWF levels were done on 107 cirrhotic patients of all aetiologies and 30 healthy controls. Mean age of patients was 52+11 years and 69% were males. Most common aetiology of cirrhosis was alcohol (40%) followed by NASH (20%), hepatitis C (16%) and hepatitis B (7%). Of 107 patients 39, 30 and 38 patients were in Child class A, B and C respectively. 40 patients had presence of venous thrombosis (35 Portal vein thrombosis, 3 Superior mesenteric vein thrombosis,

2 splenic vein thrombosis and 2 Deep vein thrombosis of lower limbs), while 67 patients were without thrombosis. Also 20, 72 and 15 patients had no varices, small varices (<5mm) and large varices (>5mm) respectively. Age, sex, Child class and size of varices had no statistically significant association with vWF levels (p value= 0.568, 0.429, 0.095, 0.604 respectively). vWF levels were higher in patients of all Child classes (mean all classes- 334%, Child class A-316%, Child class B- 308% and Child class C- 312%) compared to controls (mean- 54%), which was statistically significant(P=<0.01) . Statistically significant difference (P=0.03) of vWF levels was seen in patients with presence (n=40) or absence of thrombosis (n=67), where patients with no thrombosis had higher vWF levels. There was no statistically significant change in patients with alcohol related cirrhosis of liver compared to other aetiologies.

Table 1: Correlation of VWF assay with other variables

Variables	Correlation Coefficient	'p' Value
Age	-0.056*	0.568
Child Class	0.077**	0.433
Ogdscopy	0.070**	0.476

* Pearson Correlation Coefficient
** Spearman's rho correlation coefficient

Table2: Comparison of VWF assay w.r.t. sex

	N	Mean	Std. Deviation	'p' Value*
Male	82	327.2	122.86	0.429
Female	25	356.64	170.96	

*Unpaired't' test

Table 3: Comparison of VWF assay w.r.t. thrombosis

	N	Mean	Std. Deviation	'p' Value*
Thrombosis	40	297.45	139.63	0.03
No Thrombosis	67	355.94	128.8	

*Unpaired't' test

Table 4:

Child Class	N	Mean	Std. Deviation	95% Confidence Interval		Minimum	Maximum
				Lower Bound	Upper Bound		
A	39	316.36	140.59	270.79	361.93	32	660
B	30	308.97	110.16	267.83	350.1	96	620
C	38	372.08	142.55	325.22	418.93	192	760
Total	107	334.07	135.31	308.14	360.01	32	760

ANOVA
'p' Value=0.095

Table 5:

Varices	N	Mean	Std. Deviation	95% Confidence Interval		Minimum	Maximum
				Lower Bound	Upper Bound		
Absent	20	312.85	127.06	253.38	372.32	42	600
Small	72	334.68	137.34	302.41	366.95	32	760
Large	15	359.47	140.46	281.68	437.25	192	760
Total	107	334.07	135.31	308.14	360.01	32	760

ANOVA
'p' Value=0.604

Discussion

Portal hypertension leads to severe complications in patients with cirrhosis. Accordingly, early diagnosis of PH is crucial so that patients can be treated in a timely manner. Adequate treatment helps prevent complications related to PH and therefore helps reduce the mortality rate [2, 3]. At present, there is no perfect non invasive method to assess portal hypertension and oesophageal varices. HVPG is not always available, so a non-invasive tool to diagnose clinically significant portal hypertension would be useful. VWF-Ag can be used to diagnose for this purpose. Previous studies showed higher levels of vWF is more pronounced with higher stages of cirrhosis [4]. vWF is a non invasive predictor of portal hypertension and oesophageal varices in hepatitis B patients with cirrhosis and vWF- Ag levels correlate with liver function and hepatic venous pressure gradient and independently predict clinical outcome respectively[6,7].Our results do not show statistically significant correlation of vWF levels with Child class and size of varices. There is a statistically significant correlation seen between vWF levels and venous thrombosis, patients with venous thrombosis had lower levels of vWF levels than patients with thrombosis. Finding cannot be explained as it is thought that increased levels of vWF are responsible for increased stickiness of platelets in patients with cirrhosis to compensate for thrombocytopenia.

These contrasting results may be due to relatively small sample size of our study compared to some of the previous studies. Use of vWF levels as a predictor of severity of cirrhosis and /or development of oesophageal varices cannot be recommended at present.

Conclusion

Role of vWF levels as non invasive predictor of severity of cirrhosis and oesophageal varices is very attractive. Our study shows contrasting results from previous studies and suggests that further larger studies are needed to confirm the role of vWF levels as predictor of severity of cirrhosis.

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