

A SURVEY OF COAGULOPATHY OF LIVER DISEASE IN KARACHI

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Abstract

One hundred eleven patients divided into three groups hepatitis(53), Cirrhosis(50) and Primary liver cancer(8) cases were screened for coagulopathy by Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT). Abnormalities were found in 30% cases of hepatitis, 70% Cirrhosis and 25% cases with liver Cancer. In Hepatitis factors involving both intrinsic and extrinsic pathways were deficient specially factors IX, X and V. In Cirrhotics factors of the extrinsic pathway were severely deficient, specially factor VII, while in liver Cancer factor V and VII were deficient. Increased levels of fibrinogen were found in hepatitis and liver Cancer with low to normal in Cirrhotics. In a number of cases PT was normal though factors of the extrinsic pathway were deficient and this deficiency was manifested by prolonged APTT. This study establishes the pattern and extent of coagulopathy in liver disease in Pakistan and suggests that differences observed in comparison to Western populations are due to differences in etiological factors. It recommends estimation of both PT and APTT as screening tests in our population rather than PT alone, and emphasizes Vitamin K therapy in most chronic cases and those with severe hepatitis (JPMA 37: 285,1987).

INTRODUCTION

The liver plays a central role in the synthesis of several clotting factors, removal of activated factors, plasminogen activators and production of coagulation inhibitors^{1,3}. Abnormalities of the clotting mechanism in the form of deficient synthesis of clotting factors⁴, increased fibrinolysis⁵ and hypercoagulation states⁶ are well documented in both acute and chronic liver disease.⁷ Looking at our own population, liver disease in Karachi has been shown to have clinical and etiological differences as compared to the West⁸⁻⁹. These differences stem mainly from the high prevalence of Hepatitis B Virus related diseases⁸⁻⁹ and the relative lack of alcohol abuse in our population⁸. Survey of Western literature shows few studies that relate to coagulopathy in Hepatitis B Virus related acute or chronic disorders¹⁰. These etiological differences, abundance of Hepatitis B Virus related liver disorders in our population, and the lack of published literature stimulated us to undertake this study to evaluate coagulopathy in liver disease in Karachi. This paper presents baseline data on coagulopathy in three categories of liver disease: Acute Viral Hepatitis, Cirrhosis and Primary liver cancer. The pattern of coagulopathy and significance of our findings are discussed.

MATERIALS AND METHODS

One hundred and eleven histologically diagnosed patients with liver disease were screened for coagulation defects by estimating Prothrombin time (PT) and Activated Partial Thromboplastin time (APTT). Patients were divided into three groups, (1) Hepatitis 53 cases, (2) Cirrhosis 50 cases and (3) Primary liver cancer 8 cases. All these patients were at follow-up at the P.M.R.C. Research Centre, JPMC Karachi. PT was determined using calcium thromboplastin, APTT by Kaolin and Cephalin from

(Boehringer) on freshly collected plasma diluted in a 1:9 ratio of 3.8% sodium citrate to blood. Quality of tests was controlled by fresh plasma from healthy controls and commercial normal and abnormal plasmas (Boehringer). The following times were taken as normal PT 12-17 seconds, and APTT 30-38 seconds. In those cases where PT/APTF, or both, were prolonged specific factor assays were performed using factor deficient plasmas. The following were used :factors II, V, X, factors II, VII and X, factors VII and X from Sigma and Biomerieux. Factor VIII and IX and fibrinogen assay Kits from Boehringer. Calibration curves were prepared from normal fresh pooled plasmas using ratios 1:10, 1:20, 1:40, 1:80 or more, depending on kits used. Activity was plotted versus seconds for clot formation after addition of calcium thromboplastin for extrinsic factor assay and Kaolin/Cephalin for intrinsic factor assay. Using plasmas from healthy individuals the following ranges for normals were established:

Factors II, V, VII, IX and X activities 75-120%, factor VIII 75-200% and fibrinogen factor I 150-400 mg/dl. Control plasmas with and without factor deficiencies were used to control tests (Boehringer).

RESULTS

Screening for coagulopathy in the three categories of liver disease, abnormality in PT or APTT was found in about 30% of the cases with

Hepatitis, 70% of the cases with Cirrhosis and 25% of the cases with Primary liver cancer.

TABLE I
Screening for Coagulopathy in Liver Disease.

Category	PT Prolonged No. of Cases	APTT Prolonged No. of Cases	PT/APTT Prolonged No. of Cases
Hepatitis % of Total n=53	6 11.0%	10 19.0%	4 7.5%
Cirrhosis % of Total n= 50	27 54.0%	8 16.0%	4 8.0%
Primary Liver Cancer % of Total n=8	2 25%	0 0.0%	0 0.0%

Table I shows the prolongation of the two times in the three categories. Evaluation of specific factors in hepatitis patients with prolonged clotting times showed that factors V, X and IX were reduced in 80% of the cases. 15% of the cases had factors V, X and IX and VII deficiency and 5% had isolated factor V deficiency. Fibrinogen levels were on the high side and no deficiency was seen in factors II and VIII. In 4 cases with prolonged APTT, low activity of factors V and X were found with normal PT.

TABLE II
Factor Assays in Hepatitis.

	Fibrinogen I mg/dl	II	%Activity of Factors Range of Activity in ()				Mean \pm SD	IX
			V	X	VII	VIII		
PT Prolonged n=6	430 \pm 68.1 (350-520)	100 \pm 14 (80-120)	68 \pm 22 (40-100)	73 \pm 25 (40-100)	81 \pm 26 (40-110)	143 \pm 42 (100-180)	98 \pm 11 (80-110)	
APTT Prolonged n=10	456 \pm 73 (350-500)	96 \pm 13 (80-120)	59 \pm 18 (40-100)	56 \pm 23 (20-90)	97 \pm 10 (80-110)	188 \pm 68 (100-280)	86 \pm 26 (40-110)	
PT/APTT Prolonged n=4	442 \pm 80 (350-520)	98 \pm 17 (80-120)	58 \pm 17 (40-80)	60 \pm 16 (40-80)	98 \pm 10 (90-110)	125 \pm 36 (100-180)	105 \pm 6 (100-110)	

Table II details factor activities in various situations in hepatitis cases.

Evaluation of specific factors in Cirrhotics with prolonged clotting times showed that 60% of the total cases had factor VII deficiency, 30% had factor VII, V and II deficiency and 10% had deficiencies of both intrinsic and extrinsic pathways with deficiencies of factors I, II, V, VII, IX and X Fibrinogen levels were low to normal and all other factors were affected in various degrees in terms of activity except factor VIII which was normal. Similar to cases with hepatitis, 3 cases with prolonged APTT and normal PT had deficiency of extrinsic pathway factors except VII.

TABLE III
Factor Analysis in Cirrhotics.

	Fibrinogen I mg/dl	II	% Activity of Factors (Mean \pm SD) Range of Activity in ()				IX
			V	VII	X	VIII	
PT Prolonged n=27	204 \pm 130 (60-450)	80 \pm 25 (40-111)	82 \pm 20 (60-110)	77 \pm 24 (40-120)	85 \pm 19 (60-110)	166 \pm 32 (100-260)	84 \pm 19 (60-110)
APTT Prolonged n=7	180 \pm 141 (60-400)	75 \pm 28 (60-110)	75 \pm 22 (50-100)	80 \pm 20 (60-110)	70 \pm 17 (50-100)	162 \pm 40 (110-230)	66 \pm 18 (50-100)
PT/APTT Prolonged n=4	92 \pm 40 (60-150)	50 \pm 12 (40-60)	58 \pm 15 (40-70)	63 \pm 13 (60-80)	65 \pm 6 (60-70)	163 \pm 57 (120-230)	58 \pm 5 (50-60)

Table III details factor activities in various situations in cirrhosis. In comparison to patients with hepatitis factor deficiencies are more marked in terms of % activity to hepatitis, factor prevalent in

cirrhosis. In our 8 cases of liver cancer only 2 had prolonged PT with normal APU. Factor analysis revealed one case with factor VII and other with factor V and X deficiency. Fibrinogen levels were high similar to hepatitis patients and no other abnormality was found.

TABLE IV
Factor Analysis in Primary Liver Cancer.

	Fibrinogen I mg/dl	II	V	VII	X	VIII	IX
	%Activity of Factors (Mean \pm SD)						
	Range of Activity in ()						
PT	450 \pm 42	95 \pm 7	75 \pm 35	75 \pm 35	85 \pm 21	155 \pm 7	105 \pm 7
Prolonged n=2	(420–480)	(90–100)	(50–100)	(50–100)	(70–100)	(150–160)	(100–110)

Table IV summarises the results in liver cancer. In all three categories in a number of patients where factor X was deficient, APTT was normal while PT was prolonged. Ten normal healthy individuals' plasmas were analysed for factor activities and their results are presented in Table V.

TABLE V
Factor Analysis in Healthy Controls.

	Fibrinogen I mg/dl	II	V	VII	X	VIII	IX
	%Activity of Factors						
Mean \pm SD	313 \pm 114	100 \pm 11	100 \pm 11	95 \pm 16	100 \pm 15	163 \pm 40	102 \pm 13
Range	(150–480)	(80–120)	(80–120)	(70–120)	(80–120)	(90–210)	(80–120)

DISCUSSION

The involvement of the liver in normal haemostatic mechanism is very complex. Hence a variety of haemostatic abnormalities can occur in liver disease. These include reduced or abnormal synthesis of clotting factors, DIC, increased fibrinolysis, Vitamin K deficiency and abnormalities of platelets. This study has primarily concerned itself with screening for coagulopathy via PT/APTT and analysis of 'factor deficiencies. The importance of coagulation abnormality lies in the fact that patient with liver disease may bleed for many reasons. Haemorrhage is usually due to local causes, such as oesophageal varices or gastritis and peptic ulceration. PT and APfl are routinely used to screen patients with liver disease and may be considered as liver function tests, occasionally being abnormal while other biochemical tests are within normal limits. With any degree of cellular damage PT and APTT will be abnormal but bleeding complication will not necessarily be present'¹¹. Generally, there is good correlation between coagulation abnormality and degree of liver failure⁴. In our series of patients the results deviate from Western experience and are rather interesting. Considering Hepatitis patients both Vitamin K dependent and independent factors are deficient with major defects in factors V, X and IX and altogether 20% of the cases had factor VII deficiency. This contrasts from Western studies where

VII is most affected and IX the least^{10,12} Furthermore factor II deficiency was not found in our cases as compared to West¹³. The point to ponder in these set of patients with Hepatitis is the large number of patients with prolonged APTT and normal PT. This raises interesting questions, since PT is the routine test of our choice in our local setup to screen coagulation defects. This prolongation of APIT was found to be due to deficiency of

factors of the extrinsic pathway. This unexplained normal PT in such cases perhaps can be explained by the fact that in invitro testing excess calcium thromboplastin is added which may overcome other factor deficiencies specially when factor II is normal in these cases and it is conversion of Prothrombin to Thrombin which controls the extrinsic pathway. Such external factors may not play a role in intrinsic pathway or the control reaction has less ability to buffer deficiencies of this pathway that we see more cases with prolonged APTT. Interesting to note in cases with Hepatitis are the high levels of fibrinogen. Synthesis of abnormal fibrinogen has 'been reported in cases of Hepatitis¹⁴, whether this phenomenon is prevalent in these cases needs to be seen. The fact that the pattern and degree of factor abnormality in Hepatitis. is different to that reported in the West, suggests that the etiological agent may determine the pattern of coagulopathy specially when the agent is a Virus which is known to alter normal cell protein synthesis. In fact differences in other parameters of liver disease have already been noted⁸.

Considering patients with Cirrhosis the degree of abnormality is remarkably high, 70% compared to Western studies 50%¹⁵. However the frequency and pattern of deficiency of clotting factors is quite similar¹⁵, with major deficiencies of the extrinsic pathway. Factors I, II V, VII and X are affected as in our study. Similar to patients with Hepatitis a number of cirrhotics had deficiencies of the extrinsic pathway though normal PT and prolonged APTT. We are at pains to offer the same argument as in cases with Hepatitis since prothrombin factor II was deficient in many of these cases. Whether excess thmomboplastin or some other factor is responsible for this phenomenon needs to be investigated.

Finally,

compared to studies on Western cirrhotics, factor deficiencies of the intrinsic pathway are less frequent in our cases.¹⁶ These differences can again be attributed to the etiological agent in our population.

These observations on coagulopathy, and those of others on our cirrhotics⁸ that relate to clinical status, suggest a poorer prognosis of our patients. However the high prevalence of Vitamin K dependent factor deficiencies may counter this bad prognosis via Vitamin K therapy. Literature is scanty on studies related to coagulopathy in primary liver cancer¹⁷. The coagulopathies seen in few of our cases are limited to the' extrinsic pathway. Since many of these cases have associated cirrhosis, this low frequency of coagulopathy is surprising. In presence of the observed factors VII, V and X deficiency we would also expect other deficiencies as in our cirrhotics. Is the malignant cell capable of hyper-production of clotting factors? This is certainly true for fibrinogen as in our cases and hence able to overcome many factors deficiencies prevalent in recent cirrhotic. These are interesting speculations on a few patients though the fact remains that there are haemostatic defects in Ca liver.

Our study is deficient in the sense that we have not considered contact factors whose levels are reduced in liver disease¹⁸ Technically such assays are difficult and clinically it is unlikely that this observation is significant since even severe congenital deficiency of these factors gives rise to surprisingly few bleeding problems¹⁸ We have also not considered elements of fibrinolysis in cases with low fibrinogen, DIC, Plasminogen or anti-thrombin levels. These would no doubt throw light on the mechanism of the observed factor deficiencies. Indeed in the light of our findings it would be worthwhile to study these mechanisms in our population with liver disease.

We conclude that keeping with complex involvement of the liver in the coagulation mechanism, abnormalities are prevalent in our population with livçr disease. However 'the pattern and degree of abnormality is strikingly different from the Western population. We suggest both PT and APTT as screening tests in our patients with Hepatitis and Cirrhosis. Furthermore we suggest Vitamin K therapy

in cases of Cirrhosis, since in many cases PT is normal in presence of deficiencies of Vit K dependent factors.

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