ORIGINAL ARTICLE

MEDICAL CONDITIONS ASSOCIATED WITH PROLONGED ACTIVATED PARTIAL THROMBOPLASTIN TIME IN SWAT

Mukamil Shah, Imran ud Din Khattak, Sania Tanweer Khattak, Abdul Ahad, Muhammad Amin Jan Mahsud

Department of Pathology, Gynae /Obs, & Medicine, Saidu Medical College, Swat and Department of Pathology, Gomal Medical College, D.I.Khan, Pakistan

ABSTRACT

Background: APPT is a commonly requested laboratory test in various bleeding conditions and as a screening test preoperatively. It is also used to monitor heparin therapy. This study was conducted to see the frequency of various medical conditions presenting with prolonged activated partial thromboplastin time (APTT).

Methodology: This prospective study was conducted in Department of Pathology Saidu Medical College, Shah Clinical laboratory, Saidu Sharif, Swat, Pakistan from July 1, 2009 to June 30, 2010. One hundred patients (59male and 41 female) with APTT>10 seconds of the normal pooled plasma control were studied. Those on anticoagulants therapy were excluded from the study. Ethyelenediamine tetra acetic acid and citrated blood samples were taken for tests to be performed. Blood counts were performed on Coulter Counter Haematology analyser. APTT, Prothrombine time, Bleeding time and Thrombin time were performed manually.

Results: Out of 100 patients, liver disease was present in 39(39%); 19 males and 20 females, disseminated intravascular coagulation in 20(20%); 6 males 14 females, Haemophilia A in 20(20%), Haemophilia B in 8(8%) and miscellaneous in 13(13%); 6 males and 7 females.

Conclusion: APTT test should be included in the investigations for screening in bleeding tendencies and preoperatively to prevent fatal haemorrhage. In order of frequency the commonest causes of prolonged APTT in our set up are liver disease, followed by DIC, Haemophilia A, and Haemophilia B.

KEY WORDS: Activated partial thromboplastin time, Haemophilia, Disseminated intravascular coagulation, Liver disease.

INTRODUCTION

A coagulation defect may be present when measure time of a coagulation based test is above the 95% of confidence limit of normal reference range. Activated partial thromboplastin time (APPT) was devised by Longdell Wagnar and Brinkhus as a measure of the intrinsic pathway.[1] APTT is used to asses over all competency of the intrinsic pathway of coagulation; an abnormal value may be caused by any of several abnormalities along this pathway or by many other variables including the presence of inhibitor, poor collection of the sample or variables in the laboratories.[2]

APTT determines the time in which plasma previously incubated with kaolin or other surface active agents takes to clot in the presence of an optimum amount of platelets lipid substitute and calcium.[3] APPT is a commonly requested laboratory test in various bleeding conditions and as a screening test preoperatively. It is also used to monitor heparin therapy.

APTT is said to be increased when the patient value is >10 second of the normal control. It is increased in congenital and acquired conditions. The congenital diseases are Haemophila A, Haemophilia B, von-Willibrand's disease, afibrinogenemia and dysfibrinogenemia. The acquired conditions are disseminated intravascular coagulation (DIC), liver disease, renal diseases and coagulation inhibitors.[4]

MATERIAL AND METHODS

A total number of 100; 59 males and 41 females were included in the study. The subjects were obtained from various wards of Saidu Group of teaching hospitals and consultants clinics at Saidu Sharif Swat, from July 1, 2009 to June 30, 2010. Patients of any age group and sex with pro-

longed APTT were included and those on heparin or other anticoagulant therapy were excluded from the study. Twenty-five healthy subjects were taken in this study as normal controls.

All the investigations were done at Saidu Medical College and Shah Clinical Laboratory Saidu Sharif Swat. EDTA and citrated blood samples were taken for tests to be performed. Blood counts performed on Coulter counter Haematology analyser. APTT, PT, TT and BT were performed manually.

The Computer software SPSS version 12.0 was used for the analysis of data.

RESULTS

In this study 100 patients with prolonged APTT were included. The patients were taken from various wards of Saidu Group of Teaching Hospitals and consultant clinics at Saidu Sharif, Swat. Twenty-five normal individuals were included as controls. APTT was considered to be prolonged when the patient value was >10 seconds of normal control.

Mean ages of Haemophilia A patients were 19.45+2.0 years and of Haemophilia B patients 23.25+3.10 years. Liver disease patients belonged to a higher age group (mean age of males 38.5+2.96 years and females 47.00+2.76 years). In DIC patients mean age was 28.83+5.56 and 31.6+3.6 years in males and females respectively. The miscellaneous group comprised von-Willebrand disease (2), non-Hodgkin lymphoma (2), fibrinogen deficiency (2), dysfirinogenemia (2), inhibitors (4) and renal disease (1). The results of patients and controls are shown in Tables 1 to 3.

Table1: Occurrence of Prolonged Activated Partial Thromboplastin Time in Different Disorders.

Gender	Liver Disease	Haemophilia A	Haemophilia B	DIC	Miscellaneous
Male (59)	19 (19%)	20 (20%)	8 (8%)	6 (6%)	6 (6%)
Female(41)	20 (20%)	—	—	14 (14%)	7 (7%)
Total(100)	39 (39%)	20 (20%)	8 (8%)	20 (20%)	13 (13%)

Table 2: Prothrombin time, Activated partial thromboplastin time, Thrombin time, and Bleeding time of control and different patient groups.

Group	PT Sec. Mean+SEM	APTT Sec. Mean+SEM	TT Sec. Mean+SEM	BT min. Mean+SEM
Control				
Male(19)	13.36+0.124	35.50+0.224	10.0+0.183	6.67+0.50
Female(06)	13.20+0.147	35.60+0.33	10.4+0.242	3.45+0.56
Haemophilia A				
Male (20)	14.56+1.23	117.6+5.8****	10.24+0.211	3.8+1.38
Haemophilia B				
Male (08)	15.4+0.18	88.50+7.7**	10.38+0.375	3.50+0.40
Liver Disease				
Male (19)	26.84+1.62**	79.3+4.2***	12.47+0.62*	5.0+1.20
Female (20)	24.85+2.37**	69.6+13.6**	12.70+0.98*	5.2+0.73
DIC				
Male (06)	22.83+0.166**	112.50+3.09**	18.83+0.98**	22.3+2.3***
Female (14)	20.83+0.116***	105.00+4.90*	16.21+0.434**	22.7+1.4***
Miscellaneous				
Male (06)	18.85+1.86**	91.4+9.5**	12.14+0.72	3.40+0.42
Female (07)	20.87+2.10**	110.0+6.2*	10.33+0.30	5.54+1.4

*p<0.05 as compared to respective control, **p<0.01 as compared to respective control, ***p <0.001 as compared to respective control, ****P<0.01 as compared to Haemophilia B and Liver Disease and DIC Group.

Table 3: Bleeding Time, Haemoglobin, Total Leukocyte Count, and platelets count in control and different patient groups.

Group	Bleeding Time Min Mean+SEM	Haemoglobin g/dl. Mean+SEM	TLC X10^6/L. Mean+SEM	Platelets x10^6L Mean+SEM
Control				
Male (19)	4.67+0.50	12.95+0.19	6.7+0.37	2747+9.3
Female (06)	3.45+0.0.56	121+0.22*	6.2+0.33	219.22+12.94
Haemophilia A				
Male (20)	3.8+1.38	12.16+1.89	6.33+0.46	209+10.29***
Haemophilia B				
Male (08)	3.50+0.40	12.65+0.33	8.46+1.26	191.62+39.26
Liver Disease				
Male (19)	5.0+1.20	10.69+0.40	7.1+0.95	170.21.7***
Female (20)	5.2+0.73	9.93+0.82	4.08+0.95	93.35+12.0***
DIC				
Male (06)	22.3+2.3***	12.1+0.33***	9.4+1.4**	19.0+5.1****
Female (14)	22.7+1.4***	11.6+0.23***	9.9+1.2***	26.8+4.9****

*P<0.05 as compared to respective control, **P<0.01 as compared to respective control, ***P <0.001 as compared to respective control, ****P<0.01 as compared to respective control.

DISCUSSION

In the present study of 100 cases with prolonged APTT, patients were assigned to various aetiological groups by specific investigations. Haemophilia A was seen in 20% males and Haemophilia B in 8% males in our study. Incidence of Haemophilia A has been reported in Western population to be 5 to 10 times greater than Haemophilia B, which has incidence of 1 in 5000 and 1 in 50,000 respectively.[5] A study from India describes 42.4% of the patients with coagulation defects having Haemophilia A.[6] Windyga et al after reviewing 3224 patients with inherited blood coagulation disorders have reported 46.9% having Haemophilia A and 7.4% Haemophila B.[7]

In the present study 39% of patients with prolonged APTT had chronic liver disease. Raised PT and APTT in liver disease has been reported by many workers and is attributed to decreased synthetic capacity of liver resulting in reduction of coagulation factors.[8,9] However in many cases a marginal increase in APTT may be seen.[10]

In the present study 20% patients had disseminated intravascular coagulation (DIC), out of which 70% were females. Raised APTT does not reflect true incidence of DIC in patients as increase in APTT is seen only in 50% to 85.7% patients of DIC.[5,11] Raised APTT and bleeding episodes have been reported in 87% patients of acute DIC, while in chronic DIC, PT and APTT may be normal and the underlying cause of DIC may affect the laboratory findings.[12]

In the present study mean age of Haemophilia A patients was 19.45+2.0 years and of Haemophilia B patients was 23.25+3.10 years. In haemophiliacs congenital defect is often discovered by a prolonged episodes of bleeding after minor injuries.[13] A considerable higher mean age of 30.9 years for Haemophilia A and 29.2 years for haemophilia B has been reported from Europe.[7] A higher mean age of haemophilia patients in developed countries may be due to better emergencies / medical facilities available to these patients.

In the present study liver disease patients belonged to a higher age groups (mean age of males 38.5+2.96 years and of females 47.00+2.76 years which is lower than many studies reports on chronic liver disease.[14,15]

In this study DIC patients mean ages were 28.83+5.56 and 31.6+3.6 years in males and females respectively. There is consensus that DIC may occur at any age.[2,10,11,16]

In the present study mean haemoglobin in Haemophilia A was significantly (p<0.05) lower than controls, although degree of anaemia was not remarkable. Anaemia has been described as a common feature of Haemophilia A but haemoglobin level varies with degree and proximity of bleeding episodes.[3,17]

In the present study liver disease patients showed a significant (p value <0.05) lower level of haemoglobin as compared to normal controls. Anaemia in chronic liver disease has been reported

to be post haemorrhagic or due to hypoplastic bone marrow, viral infections and shortened red cells life span. Folate deficiency in alcoholic cirrhosis, haemolysis due to congestive splenomegaly or lipid disturbances may also contribute towards anaemia.[18]

In disseminated intravascular coagulation (DIC) haemoglobin in male patients was significantly ($P<0.05$)lower than controls. Anaemia is not a consistent feature of DIC as quoted by many workers.[1]

In this study, in DIC group 19 out of 20 patients had bleeding tendency while all 20 patients had petechial spots. In DIC cases 87% has been reported to have some sort of bleeding mainly due to depletion of clotting factors and platelets.[19] However in DIC patient a significantly higher than control TLC was recorded. A high TLC has been reported in DIC patients.[20]

In this study female with liver disease and male and female with DIC, platelets counts were below normal limits and were highly significantly ($p<0.001$) lower than controls. A moderately low platelets counts has been described in earlier studies.[9,10] A decrease platelets count in DIC patients has been well documented.[1,17] Similarly PT&TT were also prolonged in DIC.

CONCLUSION

APTT test should be included in the investigations for screening in bleeding tendencies and preoperatively to prevent fatal haemorrhage. In order of frequency the causes of prolonged APTT in our set up are liver disease, followed by DIC, Haemophilia A, and Haemophilia B.

REFERENCES

1. Bern RM, Levy MN. Heamostasis and blood coagulation in physiology. Toraranto CV Mosby company 1983; p.411-35.
2. Kitchen C. Activated partial thromboplastin Time of unknown etiology. Am J Heamatalogy 1988;27:38-45.
3. Laffan M, Mine R. In: Dacie JV, Lewis SM (eds). Practical heamatology. 10th ed. 2006; p.380-401.
4. Eritsma, George A. Laboratory evaluation of heamorrhage and thrombosis: Diagnostic Heamotology WB Saunders Company Philadelphia London Toranto 1995; 564-566,1564-6.
5. Triplett DA.Coagulation and bleeding disorders: review and update. Clin Chem 2000 ;46:1260-9.
6. Gupta M, Bhallacharyga M, Choudhry VP, Savena R. Spectrum of inherited bleeding disorders. Clin Appl Thromb Hemost 2005:11:325-30.
7. Windyga J, Lopaciuk S, Stefanska E, Klukowska A. Hemophilia and other inherited blood coagulation disorders in Poland. Pol Arch Med Wewn 2004:112:1197-202.
8. Knapp DD. Erythrocyte abnormalities. In: Stiene-Martin Ja ed. Clinical Haematology 2nd ed. Lippincott 1998;p.10-35.
9. Dessai HG, Naik AS. Acute Viral E hepatitis with chronic liver disease (autoimmune hepatitis). Gastroenterology 2005: 58:113-5.
10. Piscaglia F, Ciringo S, Hermida RC, Valgimigli M, Donut G, Pulareti G, et al. Diurnal changes of fibrinolysis in patients with liver cirrhosis and esophageal varices. Hepatology 2000;31:349-57.
11. Borgognone A, Gherardini G, Marinelli F. Disseminated intravascular coagulation as the underlying cause of multiple organ failure in burned patients: Preliminary observations. Annals MBC 1991;4:57-64.
12. Toh. CH and Dennis M. Disseminated intravascular coagulation : old disease, new hope. BMJ 2003;327:974-7.
13. Soucie JM, Evatt B, Jackson D and The Hemophilia Surveillance system Project Investigators. Occurrence of hemophilia in the United States. Am J Hematol 1998;59:288-94.
14. Kaplam MM. Primary billiary cirrhosis. New Eng J Med 1996;355:1570-80.
15. Silini M, Bottelli R, Asti. Hepatitis C virus genotypes and risk of hepatocellular carcinoma in cirrhosis: a case control study. Gastroenterology 1996;111:199-205.
16. Ho CH, Hou MC, Lin HC, Lee SD, Liu SM. Can advanced hemostatic parameters detect disseminated intravascular coagulation more accurately in patients with cirrhosis of the liver? .Zhonghaua Yi Xue Za Zhi 1998;61:332-8.
17. Mahasandana C, Patharathienskul D, Suvatte V. Haemophilia with Factor VIII and factor IX inhibitors, incidence, bleeding problems and management. Southeast Asian J Trop Med Public Health 1993;24 Suppl 1:106-12.
18. Rieghetary MT, Davey FR. Erythrocytic disorders. In: Hanry JB ed. Clinical Diagnosis and managements by laboratory methods. WR Saunders Company 2001.p.551-5.
19. Warr TA, Rao LVM, Rapaport SI. Disseminated intravascular coagulation in rabbits induced by administration of endotoxin or tissue factor: effects of anti tissue factor antibodies and measurement of plasma extrinsic pathway inhibitor activity. Blood 1990;75:1481-9.
20. Tondi T, Yarat A. 6,7-Dihydroxy-3-phenyl-coumarin inhibits thromboplastin induced disseminated intravascular coagulation. Br J Haematol, 2004;126:226-30.

Corresponding author:

Dr. Mukamil Shah
Assistant Prof. Department of Pathology
Saidu Medical College
Swat, Pakistan
E-mail: drmukamil_shah@yahoo.com