ANTI-THROMBIN III LEVELS IN SOME MALAYSIAN PATIENTS SUSPECTED OF HAVING ACQUIRED COAGULATION DISORDERS

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SYNOPSIS

Anti-thrombin III values were determined in thirty-six patients with coagulation problems associated with DIC and sepsis, thrombosis and other miscellaneous symptoms. Of these, AT III values were low in eight patients. Six of these patients had low fibrinogen degradation products (FDP) and abnormal coagulation profile while two of the patients had normal coagulation profile and normal FDP. The usefulness of AT.III estimation in the investigation of bleeding and thrombotic disorders is discussed.

INTRODUCTION

Anti-thrombin III (AT.III) is a principal coagulant inhibitor of plasma that neutralises thrombin and inhibits the serum proteases involved in the intrinsic clotting system (1, 2). It is the only protein whose concentration is directly correlated with thrombotic diatheses and it has been shown to be the heparin cofactor (1, 3). Diminished AT.III may occur as a congenital or acquired condition (4, 5).

Detailed families with diminished AT.III levels and the high incidence of thromboembolism in these families have been reported (6, 7, 8, 9, 10). A lower level of AT.III was also noted in post-operative patients (11, 12). Women on oral contraceptives too seem to have lower plasma AT III values (13, 14, 12). Liver diseases, active thrombosis and pregnancy are all associated with a decrease in AT III value (15, 16). AT III is also reduced in disseminated intravascular coagulation (DIC) (17).

Excessively low levels (pressumably due to the effectiveness of consumption of protein during the clotting process) may compromise the effectiveness of heparin anticoagulant if heparin is chosen to treat the condition. In view of the above reports a study was made to assess the usefulness of estimating AT III levels in suspected coagulation disorders in some Malaysian patients.

Table I: AT III, FDP values and coagulation profiles of patients with suspected acquired coagulation disorders

Patient	Age/Sex	Diagnosis	Fibrinogen degradation product (ng/ml)	Coagulation profile	AT III (%)
1	25/F	Pre-eclampsia with intrauterine death and abruptive placenta	N	N	110
2	11/12/M	Head injury	N	N	148
3	49/M	Stroke, transient ischaemic attack	N	N	90
4	46/M	Myocardial infarction	N	N	170
5	33/F	Missed abortion	N	N	100
6	25/F	Lower section caesarian section	N	N	115
7	48/F	Intrahepatic stone	N	N	210
8	26/M	Haematuria, aspirin defect	N	N	205
9	30/F	Missed abortion	N	N	250
10	34/F	Haematuria	N	N	120
11	28/F	Purpura simplex	N	N	160
12	6/12/M	Purpura	N	N	145
13	72/M	Bleeding after tooth extraction, on prednisolone for 6 yrs. Stopped since 1981	N	N	80
14	44/F	Deep vein thrombosis	N	N	75
15	31/F	Disseminated intravascular coagulation	N	N	75
16	24/F	Cerebral thrombosis	N	N	190
17	17/F	Sinus thrombosis	N	N	200
18	63/F	Sinus thrombosis (patient heparinised)	10-40	Abnormal (prolonged)	80
19	69/F	Diabetes, Hypertension	N	N	25↓
20	48/F	Superficial thrombosis of veins	N	N	55↓
21	68/F	Chronic monocytic leukaemia	10-40	N	150
22	21/F	Myasthenia gravis	10-40	N	137
23	72/M	Gastric ulcer	> 40↑	N	78
24	30/F	Chronic renal failture	> 40↑	N	113
25	69/F	Bleeding duodenum	> 40↑	N	63
26	75/N	Disseminated intravascular coagulation	> 40↑	N	130
27	38/N	Lower section caesarian section with DIVC	> 40↑	N	65
28	33/F	Malaria with intrauterine death	> 40↑	N	100
29	56/F	Pelvic vein thrombosis post-operatively for carcinoma of ovary	> 40↑	N	100
30	26/F	Immune thrombocytopenia, purpura	> 40↑	N	145
31	21/F	Malaena, haematuria, septicaemia with renal failure	> 40↑	Abnormal	55↓
32	33/M	Acute promyelocytic leukaemia with disseminated intravascular coagulation and septicaemia	> 40↑	Abnormal	50↓
33	-/F	Diabetes with infection, disseminated intravascular coagulation and gastrointestinal bleeding	> 40↑	Abnormal	45↓
34	24/F	Petechial haemorrhage,gram(-) septicaemia with burns and disseminated intravascular coagulation	> 40↑	Abnormal	35↓
35	3/7/F	Septicaemia with disseminated intravascular coagulation	10-40	Abnormal	*33↓
36	53/M	Diabetes, cirrhosis and disseminated intravascular coagulation, infection	> 40↑	Abnormal	10↓

***AT III value is about half that of adults. Matured level is reached at about 12 months (26)**
N = Normal

Table II Abnormal coagulation profile and platelet counts of patients 31-36 with low AT III values. * = Abnormal Value, NR = Normal Range, ND = Not done.

ients	Bleeding Time (NR = within 3 min)	Whole Blood Coagulation Time (NR = 5-11 min)	Prothrombin Time (NR = 11-36 sec)	Partial Thrombo-plastin Time (NR = 35-45 sec)	Thrombin Time (NR = 17-24 sec)	Fibrinogen Concentration (NR = 150-450mg%)	Fibrinogen Degradation Products (NR = Below 10ng/ml)	Platelets (NR = 150-350x10^9/L)
31	>10*	17*	60*	>120.0*	31*	220* (transfused cryoprecipi-tate)	>40*	80* x 10^9
32	>10*	9½	17.4*	43.6	16.8	350	> 40*	10 x 10^9
33	8½*	4½	27*	73*	44*	< 100*	> 40*	133 x 10^9*
34	6½*	7	20*	53*	16	450	>40*	4 x 10^9*
35	ND	3	19.4*	51.4*	28.6*	185	10-40	73 x 10^9
36	>10*	15*	210*	300*	57.8*	not detectable	10-40	6 x 10^9*

MATERIALS AND METHODS

Whole blood from patients are collected into plastic tubes in the ratio of nine parts of blood to one part of 3.8% sodium citrate solution. Within 30 minutes of collection platelet-poor plasma from the citrated whole blood was prepared by centrifugation at 15,000xg for 15 minutes. Immediately after centrifugation the plasma was stored in plastic tubes at (-)30°C. AT III was assayed by using an assay which involved a synthetic chromogen as substrate for thrombin (Quantichrom AT III, Abbot Laboratories). The colour produced was measured with the Pye Unicam SP 30 at 405nm. Tests for coagulation profile include the following tests:-

Whole blood coagulation time
Bleeding time
Clot retraction
Clot stability test for Factor XIII
Prothrombin time
Kaolin partial thromboplastin time
Thrombin time
Fibrinogen concentration

The patients were sent for coagulation studies because all had coagulation problems and the cases were diagnosed on clinical and laboratory findings.

Normal AT III values in our laboratory are taken as 60% and above (unpublished data).

RESULTS

The AT III values, FDP and coagulation profiles of patients suspected of having coagulation disorders are shown in Table I. Most of the thirty-six patients who presented with coagulation problems had normal coagulation profiles with normal AT III levels.

Ten patients had high FDP, normal coagulation profile and normal AT III levels while six patients had high FDP, abnormal coagulation profile and low AT III values. It is interesting to note that all six patients (No. 31-36) with low AT III had DIC secondary to infection. Two (No. 17, 18) had cavernous sinus thrombosis, one (No. 16) had cerebral thrombosis and one patient (No. 29) had pelvic vein thrombosis post-operatively. Three of these patients (No. 16-18) had normal coagulation profile, FDP and AT III values while the fourth patient (No. 29) had high FDP but normal coagulation profile and normal AT III value.

The coagulation profiles and platelet counts of patients No. 31-36 are shown in Table II.

DISCUSSION

The maintenance of blood in a fluid state within the blood vessels is dependant upon a well-balanced haemostatic mechanism. This requires an intact vasculature, sufficient circulating platelets having proper function, adequate levels of the plasma protein clotting factors, a functioning fibrinolytic system and adequte inhibitory substances to keep the coagulation related enzymes in check (18). One of these inhibitors is AT III.

AT III is a plasma alpha 2 globulin, synthesized in the liver, (19). Its main physiologic role is in the inactivation of activated factor X and it is at this site within the coagulation cascade that it exerts its most critical anticoagulant effect (20.1). As well as being the naturally occuring inhibitor to thrombin, factor Xa and other coagulation enzymes, AT III is the heparin cofactor (1, 3). It has been demonstrated that the anticoagulant effect of exogeneously administered heparin is dependent upon its complexing with AT III. Once the AT III — heparin complex is formed, all thrombin-mediated reactions in the clotting system are inhibited (21).

The clinical significance of reduced levels of AT III and correlation with thrombotic disease was first described by Egeberg (4). Thrombotic symptoms often evidenced in young adults and affected individuals are reported to have levels of AT III ranging from 40% to 60% of normal (4). Such diminished levels may occur as a congential or acquired condition (4, 5). Some of the conditions in which acquired deficiencies of AT III have been noted are severe cirrhosis (22), disseminated intravascular coagulation (17), pulmonary embolism (10, 17), and post-surgically (11, 12).

Very low levels of both AT III and alpha 2 macroglobulin were found in patients with DIC accompanied by sepsis (17). Our results agreed with the above report in that AT III in six of our patients with DIC secondary to infection was low. It has been reported that in cerebral thrombosis normal AT III values were found (23, 24). Patients No. 16-18 seem to fit into this category in that all had cerebral thrombosis but had normal AT III levels. Patient No. 29 had a pelvic vein thrombosis and normal AT III value. It has been reported that in deep vein thrombosis (DVT) AT III value is only sometimes temporarily decreased (25), indicating that the time at which AT III is assayed is critical. In contrast to deep vein thrombosis, in congenital AT III deficiency, AT III is always low (6, 10).

From this study, there appears to be a group of patients suffering from disseminated intravascular coagulation

associated with sepsis who consistently show a lowering of AT III values. Administration of purified AT III has been proposed in patients with DIC who have low AT III (25).

It also appears from this study that the investigation of AT III is useful in identifying patients with risk of thrombosis associated with a deficiency of AT III. The patient No. 20 who has a low AT III but normal coagulation profile and FDP may have a congenital AT III deficiency. This patient has a history of recurrent superficial venous thrombosis, occuring in her hands and calf. Hereditary deficiency has not been described in the Malaysian population and the finding of this patient with a low value indicates that this condition warrants further attention. Patient No. 19 has a low AT III deficiency associated with diabetes.

The tendency to thrombosis in patients with AT.III deficiency may be controlled with oral anticoagulants of the coumarin type on a long term basis. If heparin is used in the management of patients with low AT.III, it would be desirable to restore AT III levels by infusion of AT III concentrates or plasma, in order to obtain sufficient anticoagulation.

ACKNOWLEDGEMENTS

This work was partially supported by a grant to S.H. Ton by the National University of Malaysia. We are grateful to Cik Absiah for typing the manuscript.

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