ORIGINAL ARTICLE

FREQUENCY OF ACQUIRED ANTI-THROMBIN III DEFICIENCY IN PATIENTS WITH DISSEMINATED INTRAVASCULAR COAGULATION

Ammar Bin Saad, Shahtaj Masood*, Javed Iqbal Khan, Sadia Taj***, Ali Raza†, Sohail Ahmad Malik††**

Department of Pathology, Ayub Medical College, Abbottabad, *Department of Pathology, Hayatabad Medical Complex, Peshawar, **Department of Surgery, Abbottabad International Medical College, Abbottabad, ***Fatima Memorial Hospital, College of Medicine and Dentistry, Lahore, †Department of Pathology, Sahara Medical College, Narowal, ††Department of ENT, Ayub Medical College, Abbottabad, Pakistan

Background: Anti-thrombin III (AT III) is a glycoprotein consists of 432 amino acids which inactivates several enzymes of coagulation system. Acquired AT III deficiency is observed in a condition when activation of coagulation system is inappropriate like Disseminated Intravascular Coagulation (DIC). This study was conducted to determine the frequency of anti-thrombin III deficiency in patients with DIC. **Methods:** This cross-sectional descriptive study was conducted in Hayatabad Medical Complex Peshawar from October 2014 to April 2017. A total of 136 patients were included in the study. Consecutive, non-probability sampling was performed. Diagnosed patients of disseminated intravascular coagulation (DIC) of both genders aged 18–60 years with D-dimer >1,000 ng/dl were included. Patients with coagulation abnormalities other than DIC were excluded. Chromogenic determination of AT III was done. **Results:** Mean age of the patients was 45±10.8 years, males were 60%, and females were 40%. D-dimer level range was 1,000–2,000 ng/dl in 59% cases and >2,000 ng/dl in 41% cases. Mean D-dimer levels was 2,000±207.1 ng/dl. Anti-thrombin deficiency was present in 22.79% patients. **Conclusion:** The frequency of acquired anti-thrombin deficiency was found to be 22.79% in patients with disseminated intravascular coagulation.

Keyword: anti-thrombin III, deficiency, disseminated intravascular coagulation, DIC

Pak J Physiol 2019;15(4):35–7

INTRODUCTION

The coagulation system of human body, is activated in response to injury and is inactivated by Anti-thrombin III (AT III), a 432 amino acids containing glycoprotein.[1] The normal concentration of AT III in plasma is approximately 0.12 mg/ml to 0.2 mg/ml.[2] The reference range of anti-thrombin in adults is 80–120%.[3] Acquired AT III deficiency is due to situations where activation of coagulation system is inappropriate like Disseminated Intravascular Coagulation (DIC), microangiopathic haemolytic anaemia due to endothelial damage (haemolytic uremic syndrome) and venoocclusive disease (VOD) in patients undergoing bone marrow transplantation.[4] The estimated incidence of inherited AT III deficiency is 1:2,000–1:5,000 in normal population, which are either type I or type II depending upon functional and immunochemical AT III analysis.[5]

Disseminated intravascular coagulation (DIC) occurs due to systemic activation of blood coagulation system, which results in generation and deposition of fibrin, leading to micro-vascular thrombi in various organs, and multi-organ failure.[6] Excessive circulating thrombin cleaves fibrinogen which leaves multiple fibrin clots in circulation and these clots trap platelets to become larger clots leading to micro-vascular and macro-vascular thrombosis; lodging of these clots in the vessels causing ischemia, impaired organ perfusion and end organ damage.[7]

Anti-thrombin III deficiency was determined in patients with coagulation problems associated with DIC and sepsis. In these patients, AT III deficiency was 22.2%.[8] Current insights in pathogenesis of multiple organ dysfunctions in patients with sepsis point to a pivotal role of inflammation and coagulation. One of the most important mechanisms leading to activation of coagulation in sepsis is the down regulation of anti-thrombin pathway.[9] Anti-thrombin III improves disseminated intravascular coagulation when administered to diagnosed patients.[10] Another study has shown that administration of Anti-thrombin III in patients with sepsis related disseminated intravascular coagulation is effective in shortening the duration of disseminated intravascular coagulation.[11]

This study was conducted to determine the frequency of Anti-thrombin III deficiency in patients with disseminated intravascular coagulation.

MATERIAL AND METHODS

This cross-sectional descriptive study was conducted in Hayatabad Medical Complex Peshawar from October 2014 to April 2015 after the approval from ethical review board. Sample size was calculated using WHO calculator for sample determination with 22.2% frequency of anti-thrombin III deficiency, 7% margin of error, and 95% confidence interval.[8] Sample size was calculated to be 136. Consecutive, non-probability sampling was done.

Diagnosed patients of disseminated intravascular coagulation between 18 to 60 years of both genders were included. Patients with coagulation abnormalities, history of intake of oral or intravenous anticoagulant drugs, warfarin, epinephrine, heparin, aspirin, clopidogreletc, or patients having carcinoma of liver/hepatic failure, pulmonary embolism, and history of hormonal replacement therapy (estrogens and progesterone) were excluded from study.

Venous blood was drawn from the participants and kept in a vial containing sodium citrate. It was centrifuged at 4,000 RMP for 10 min. The obtained plasma was used for estimation of anti-thrombin III levels. All tests were done using commercially available kits, keeping the temperature and other assay conditions as per guidelines of the manufacturer. Chromogenic determination of AT III was done on auto analyser (Sysmex CA 500 series).

Data was analysed using SPSS-17. Mean±SD was calculated for numeric variables. Frequencies and percentages were calculated for qualitative variables. Anti-thrombin III deficiency was stratified among age and gender to see effect modification.

RESULTS

Age distribution among 136 patients was analysed as 7 (5%) patients in age range ≤20 years, 9 (7%) patients in age range of 21–30 years, 31 (23%) patients in age range of 21–30 years, 56 (41%) patients in age range of 41–50 years, and 33 (24%) patients in age >50 years. Mean age of participants was 45±10.8 years (Table-1).

Out of the total, 82 (60%) were male while 54 (40%) were female. Four (3%) patients had Hb level <8 g/dl, 67 (49%) patients had 8–10 g/dl, while 65 (48%) patients had Hb level 10–12 g/dl. Mean Hb level was 11±9.76 g/dl. Majority of the patients (65, 48%) had TLC >20–30×10^6/L, while 37 (27%) had 10–20×10^6/L. Majority of the patients (72, 53%) had platelet count of 75–150,000, and 38 (28%) had platelet count >50–75,000. Forty-five (33%) patients had abnormal PT/APTT, 91 (67%) had normal PT/APTT normal.

Eighty (59%) patients had D-dimer level range 1,000–2,000 ng/dl while 56 (41%) patients had D-dimer level range >2,000 ng/dl. Mean D-dimer levels was 2,000±2071 ng/dl. (Table-2).

Anti-thrombin deficiency was present in 31 (23%) patients and was absent in 105 (77%) patients. (Table-3).

Table-1: Age distribution (n=136)

Age	Frequency	Percentage
≤ 20 years	7	5
21–30 years	9	7
31–40 years	31	23
41–50 years	56	41
>50 years	33	24
Total	136	100

Table-2: D-dimer levels (n=136)

D-dimer levels	Frequency	Percentage
1,000–2,000 ng/dl	80	59
>2,000 ng/dl	56	41
Total	136	100

Table-3: Stratification of Anti-thrombin III deficiency with respect to age (n=136)

Age (Years)	ANTI-THROMBIN DEFICIENCY		
	Present	**Absent**	**Total**
≤20	1	6	7
21–30	2	7	9
31–40	7	24	31
41–50	14	42	56
>50	7	26	33
Total	31 (23%)	105 (77%)	136 (100%)
(Chi square) p	0.9742		

DISCUSSION

Anti-thrombin III (AT III) is a glycoprotein; it inactivates several enzymes of coagulation system. The normal concentration of AT III in plasma is approximately 0.12–0.2 mg/ml. The reference range of anti-thrombin in adults is 80–120%. Acquired AT III deficiency is observed in situations where activation of coagulation system is inappropriate. Disseminated Intravascular Coagulation (DIC) is one of these conditions.

All patients in this study had quantitative analysis of AT III levels. All patients under 40 years of age had normal AT levels despite suffering from DIC due to various underlying conditions. AT III deficiency was present in all patients above 40 years of age as compared to a reference study in which AT deficiency was seen in >50 year age.[8] The age difference of the affected patients was however found to be statistically non-significant. The results were comparable with the reference study[8] regarding age distribution of the patients with AT deficiency. A similar observation has been made in other local and international studies which also report that AT levels were found to be lower in the older patients as compared to younger patients.[12–14]

Tan *et al*[8] observed AT deficiency in 18.2% males and 24% females, while in our study 23.17% males and 22.22% in females had AT deficiency. The differences, however, were non-significant, and our study was in conformity with the reference study.

In the present study 22.79% of the total patients exhibited a lower than normal levels of AT III as compared with 22.2% in the reference study[8]. Since none of the patients included in this study had any evidence of hereditary AT deficiency on the basis of their history, the decreased levels of AT were rightly attributed to acquired AT deficiency associated with different underlying and ongoing conditions. The differences were statistically non-significant and our findings were in conformity with the reference study.[8]

On correlating acquired AT deficiency with deranged coagulation profile of our patients, 70% had deranged coagulation profile (PT, APTT). Tan *et al*[8] concluded that their 85.7% patients with deranged coagulation profile demonstrated acquired AT deficiency. The differences between the ratio of patients having AT deficiency among those who had deranged coagulation profile (PT, APTT) was found to be statistically significant (p=0.002). All of our patients (100%) who had AT deficiency also had prolonged PT and/or APTT as compared with 85.7% patients in their study. It has been reported in various studies that AT deficiency was frequently associated with a deranged coagulation profile including PT and APTT.[14,15]

CONCLUSION

Frequency of acquired Anti-thrombin deficiency was found to be 22.79% in patients with disseminated intravascular coagulation.

REFFERENCE

1. Bjork I, Olson ST. Anti-thrombin. A bloody important serpin. Adv Exp Med Biol 1997;425:17–33.
2. Conard J, Brosstad F, Lie Larsen M, Samama M, Abildgaard U. Molar Anti-thrombin concentration in normal human plasma. Hemostasis 1983;13(6):363–8.
3. Maclean PS, Tait RC. Hereditary and acquired deficiency; epidemiology, pathogenesis and treatment options. Drugs 2007;67:1429–40.
4. Kuhle S, Lane DA, Jachmanns K, Male C, Quehenberger P, Lechner K, *et al*. Homozygous anti-thrombin deficiency type II and childhood thromboembolism. Thromb Haemost 2001;86:1007–11.
5. Lane DA, Kunz G, Olds RJ, Thein SL. Molecular genetics of anti-thrombin deficiency. Blood Rev 1996;10:59–74.
6. Vincet JL, De Becker D. Does disseminated intravascular coagulation lead to multiple organ failure? Crit Care Clin 2005;21:469–77.
7. Grewa Pk, Uchiyama S, Ditto D, Varki N, Le DT, Nizet V, *et al*. The ashwell receptor mitigates the lethal coagulopathy of sepsis. Nat Med 2008;14:648–55.
8. Tan SH, Doraisamy G, Noriah R, Lopez CG. Anti-thrombin III levels in some Malaysian patients suspected of having acquired coagulation disorders. Singapore Med J 1983;24:33–6.
9. Levi M, Schouten M, vander Poll T. Sepsis, coagulation and anti-thrombin. Semin Thromb Hemost 2008;34:742–6.
10. Sawamura A, Gando S, Hayakawa M, Hoshino H, Kubota N, Sugano M. Effects of anti-thrombin III in patients with disseminated intravascular coagulation diagnosed by newly developed diagnostic criteria for illness. Clin Appl Thromb Hemost 2009;5:561–6.
11. Ostemann H. Anti-thrombin III in sepsis. New evidences and open questions. Minerva Anestesiol 2002;68(5):445–8.
12. Butt JT, Tayyab M, Tasnim T. Anti-thrombin III activity and concentration in diabetes mellitus. Pak Postgrad Med J 2003;14:34–40.
13. Bick RL. Disseminated intravascular coagulation current concepts of etiology, pathophysiology, diagnosis, and treatment. Hematol Oncol Clin North Am 2003;17:149–76.
14. Napoli VM, Krzyzaniak R, Vroon DH, Newton JL. Hemostatic assay of AT III diagnostic value in 112 patients with abnormal hemostasis. Am J Clin Pathol 1985;84:173–9.
15. Fourrier F1, Chopin C, Goudemand J, Hendrycx S, Caron C, Rime A, *et al*. Septic shock, multiple organ failure, and disseminated intravascular coagulation. Compared patterns of Anti-thrombin III Protien C and Protien S deficiency. Chest 1992;101:816–23.

Address for Correspondence:

Dr. Ammar Bin Saad, Assistant Professor Haematology, Ayub Medical College, Abbottabad-22040, Pakistan.
Cell: +92-311-4549201
Email: ammarbinsaad1@yahoo.com

Received: 15 Nov 2019 **Reviewed: 10 Jan 2020** **Accepted: 21 Jan 2020**