ORIGINAL ARTICLE

INHERITED ANTITHROMBIN DEFICIENCY IN PATIENTS WITH RECURRENT THROMBOTIC EVENTS

Haroon ur Rashid, Sartaj Khan

Department of Pathology, Khyber Medical College, Peshawar - Pakistan

ABSTRACT

Objective: To investigate the frequency of hereditary antithrombin deficiency in patients presenting with recurrent thrombotic events, venous and/or arterial.

Material and Methods: This is a descriptive case series study, where a total of 145 cases with a history of recurrent thrombotic attacks, both venous and/or arterial, referred by physicians and gynaecologists of Military Hospitals (MH and CMH) to Armed Forces Institute of Pathology (AFIP) Rawalpindi and from the tertiary care hospitals of Rawalpindi and Islamabad, were included in the study, through non-probability convenient sampling. Peripheral blood samples were collected in trisodium citrate in test tube and centrifuged to obtain plasma, which was, then run in coagulation analyzer to perform functional assay (both clotting and chromogenic) and the level and activity of the Antithrombin measured and entered in the data sheet.

Results: Among 145 cases, inherited deficiency (low levels) of antithrombin was detected in nine cases with frequency of 6.2% and p value of less than 0.001. The frequency detected shows significant association between inherited deficiency of antithrombin and recurrence of thrombosis.

Conclusion: There is a definite association of hereditary antithrombin deficiency with the recurrence of thrombotic attacks.

Key Words: Heritable, thrombophilia, Natural, anticoagulant deficiency, Deep vein Thrombosis, cerebrovascular accidents, Activated protein C.

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INTRODUCTION

There is a clinical condition known as thrombophilia, in which the body has increased tendency to form blood clots or is unable to arrest clotting or to break down clots. Thrombophilia may be hereditary or acquired.[1] Deep vein thrombosis (DVT) and pulmonary embolism are major manifestations of Venous Thromboembolism (VTE) due to heritable causes, whereas, arterial thrombosis mainly presents with myocardial infarction (MI) and stroke (CVA) and these two are the most common causes of death in developed countries.[2]

Dr. Haroon ur Rashid (Corresponding Author)
Lecturer
Pathology Department, Khyber Medical College,
Peshawar - Pakistan.
Cell: 0333-9716062
Email: Haroonkhattak2049@gmail.com
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Mainly, there are two categories of the heritable abnormalities leading to increased risk of thrombosis, venous or arterial, i.e reduction in the anticoagulant function i.e. deficiency of natural anticoagulants (protein C, protein S and antithrombin) and those resulting from increased procoagulant activity i.e. factor V leiden mutation and prothrombin G20210A polymorphism.[3]

In the human blood, natural anticoagulants tightly regulate thrombin formation and its activity. Formed thrombin is directly inhibited by antithrombin and by inhibiting activated factor V (FVa) and activated factor VIII (FVIIIa) through the protein C and Protein S system, thrombin generation is down regulated and thus maintain hemostasis in a tightly regulated fashion.[4]

Deficiency of antithrombin is always inherited, but there are certain conditions in which patients may develop deficiency e.g. liver disease, severe infections, Vit K deficiency, pregnancy, those taking birth control pills or receiving hormone replacement therapy post menopause or patients on heparin or warfarin therapy. All such cases with known acquired factors were not included in this study.[5]

Hereditary deficiency of antithrombin is relatively less common, but no doubt, it is a stronger risk factor for inherited thrombophilia (Lipe Brea, et al, 2011). Recent studies conducted in USA and Europe, have suggested increased association of inherited antithrombin deficiency with arterial thrombosis leading to IHD and stroke. In our country, Pakistan, significant data is not available on the heritable risk factors of thrombophilia and paucity of data emphasizes the need of more research in this area.[6]

MATERIAL AND METHODS

This is a descriptive, case-series study, that was carried out in the Department of Hematology, Armed Forces Institute of Pathology (AFIP) Rawalpindi, Pakistan from January, 2012 to December, 2012. A total of 145 cases, with recurrent thromboembolic events, venous and arterial, fulfilling the inclusion and exclusion criteria, were included in the study, through non probability convenient sampling.

Patients, both male and female, referred by physicians and gynaecologists of the military hospitals (MH and CMH) and from the tertiary care hospitals in the Rawalpindi and Islamabad were recruited as study subjects. Only those cases were included in the study, who had already stopped anticoagulant therapy for the last 6-8 weeks, either because thrombosis had resolved or the clinician had advised them to stop anticoagulant therapy for screening and diagnostic purposes.

Patients with unexplained or recurrent episodes of DVT or pulmonary embolism CVA/strokes and heart attack, those with recurrent abortions, Intra Uterine Growth Retardation (IUGR) and other complications of pregnancy e.g. eclampsia, pre-eclampsia and abruptio-placentae and those with positive family history of natural anticoagulant deficiency were included in the study. Patients with known acquired risk factors e.g liver disease or with known heritable risk factor e.g factor V leiden mutation, were excluded in the study.

Two milliliters (2ml) peripheral venous blood was taken from each patient in a test-tube containing tri-sodium citrate anticoagulant, which was then centrifuged for 5 minutes at 34 rpm (rotation per minute). Platelet poor plasma containing coagulation factors, both procoagulants and anticoagulants (either normal or deficient) was obtained.

The resulting plasma (1.8ml) was then run in the sysmex CA-500 coagulation analyzer, to obtain functional clotting assay, to measure the antithrombin level. This was followed by chromogenic assays (functional amidolytic assays), which were carried out, separately for each patient through another analyzer, STA- compact stago coagulation analyzer. Individual readings of each assay for each sample were recorded and entered in the data sheet. The data was analyzed using statistical software, SPSS version 16 (Statistical package for social sciences, version 16).

Mean and Standard Deviations were calculated for quantitative variables like age, ethnicity and number of thrombotic events, whereas, for qualitative variables like gender (male or female), family history of inherited thrombophilia due to natural anticoagulant deficiency, deficiency of natural anticoagulants (one or more), frequency and percentages were calculated. P value was determined.

RESULTS

Inherited antithrombin deficiency was detected in nine cases out of 145 cases, giving a frequency of 6.2%. Mean age of patients was 31.37 years with Standard Deviations of 8.49. Most of the patients were in the age groups, 16-30 years and 31-45 years.

Among 145 cases, 40% were male and 60% (87 out of 145) were female. Regarding number of thrombotic attacks, majority cases i.e. 97.24 were lying in the group having 1-5 previous thrombotic events. Only small percentage (2.7%) only 4 cases, were having more than five thrombotic events in their life time so far. Regarding family history of antithrombin deficiency, only one case had positive family history of antithrombin deficiency, where, elder sister was affected.

Fifty-eight (40%) cases presented with recurrent abortions, eclampsia and IUDs, 25.5% (37 cases) presented with recurrent DVT and stroke seen in 34 (23.4%) cases. Small percentage presented with pulmonary embolism 4.8% (7 cases), Heart attacks due to IHD in 1.37% (2 cases) and thrombosis in unusual sites in 4.8% (7 cases). Inherited antihrombin deficiency was detected in nine cases in total of 145 cases. Most of the patients were young with a mean age of 28.3 years $\pm$ 6.2. Regarding gender,in nine antithrombin deficient cases, there were seven females and two males.

In nine cases, two cases had only one previous thrombotic event, one case had two events, three cases had previous three thrombotic attacks, two cases had four thrombotic attacks, experienced and only one case having more than five (5) thrombotic events experienced so far. Family history of inherited antithrombin deficiency was positive only in one case, where the elder sister had a diagnosed hereditary antithrombin deficiency and also had recurrent abortions.

Among nine cases, the deficiency was mostly detected in patients presenting with recurrent abortions, six (6) cases out of 9 cases had recurrent abortions, two

cases had recurrent stoke /CVA and only one case had thrombosis in unusual site (Portal Vein Thrombosis).

DISCUSSION

Inherited thrombophilia is considered as a multi-causal disease that results from interaction of different genetic and environmental risk factors. As a result, diverse and serious clinical disorders andthromboembolic events occur such as VTE, ischemic events such as stroke and IHD and/or obstetric complications. The severity varies with the type of inherited thrombophilic disorder. Inherited deficiency of protein C, its cofactor proteins S, and of the antithrombin were the first identified causes of inherited thrombophilia.[7] Age, positive family history and number of thrombotic attacks, were the stronger candidate factors of inherited thrombophilia resulting from antithrombin deficiency. In this study, median age of cases was 31.37 years, whereas, meanage of patients detected withantithrombin deficiency,was 28.3 years. Most of the patients were in the age group 16-30 years and 31-45 years.

The incidence of inherited thrombophilia has been reported to occur in early adulthood or below the age of 50 years. More specifically, recurrence thrombotic events due to natural anticoagulant deficiencies, have been reported to occur in the early adulthood.[8,9] The finding of age involvement in this study, is consistent with international literature.[10-12] Incidence in young age, emphasizes the need of more research in this area.

Another variable that had been studied is gender and the study reported that 40% cases were male and 60% cases were female. In 9 cases of antithrombion deficiency, there were seven females and two males. Studies have reported that both the sexes are affected equally. The findings in the study, are consistent with those in the literature.[13]

Regarding number of thrombotic attacks, the risk of recurrence reported is quite higher in patients having deficiencies of natural anticoagulants than in patients having normal levels and activity of natural anticoagulants. Thus, our finding, regarding recurrence of thrombosis, is consistent with other studies.[14,15] In our study only one case showed positive family history. Family history of heritable risk factors, especially deficiency of natural anticoagulants is extremely important and it is so important that it can be anindependent risk factor for venous thrombosis and for recurrence. The finding in our study showed little significance, which can be further evaluated with larger study group.

Regarding nature of recurrent thrombotic events, highest percentage in this study had recurrent abortions and other complications of pregnancy i.e. eclampsia and IUGR. In nine antithrombin deficient cases, majority patients had recurrent abortions (66.66%) followed by recurrent attacks of stroke (22.2%). It is evident from the study results that patients with deficiency of natural anticoagulants develop recurrence of both venous and arterial thrombotic events and more prone to develop recurrent thrombotic attacks. These findings in our study are consistent with several studies, but fewer have different results.[15]

The reported prevalence of antithrombin deficiency is one case in five hundred people to one case in five thousand people of the general population.[16] Mostly presents in heterozygous state. Homozygosity in rare and almost always fatal in utero. Different studies have reported the recurrence rates of thromboembolic events with the deficiency of natural anticoagulants differently.

In Jordan, 217 patients presenting with thromboembolic disease were tested for inherited deficiency of natural anticoagulants. It was a prospective study. Hereditary Protein C deficiency was detected in seventeen patients(7.83%), that of protein S in 15 patients(6.9%) and antithrombin deficiency in 10 patients(4.6%). 65.3% of patients with thrombophilia had positive family history of natural anticoagulant deficiency.[17]

In a local study, conducted at AFIP Rawalpindi, thirty two patients having venous thromboembolic disease were testedfor Antithrombin levels. Median age of patients was 29.1 years. 6.2% young adults were detected to have antithrombin deficiency. So, the frequency of antithrombin deficiency detected was 6.2%.[17]

At Agha KhanUniversity hospital (AKUH)Karachi,a study was conducted on 2825 patients, suspected clinically of thrombophilia. Inherited thrombophilia was diagnosed and detected in seventy patients. The frequency of protein C deficiency detected was 2.3%, that of protein S deficiency was 1.4% and that of antithrombin deficiency was 1.5%. For factor V leiden mutation, the frequency detected was 14.2% and that for homocysteinemia was 2%.[18]

In my study, high prevalence rate was observed among cases presenting with recurrent thrombotic attacks,and this is related to the high frequency of natural anticoagulant deficiency in our population. The carriers (heterozygous states) are quite common among Pakistani patients presenting with thromboembolic events, both venous and arterial, as evident from the study. These findings are supported by local study.[19]

CONCLUSION

There is definite association of hereditary antithrombin deficiency with the recurrence of thrombotic attacks.

Recommendations

Therefore, there is need of more research in this area on larger scale and also there is need of increased screening for this important risk factors in selected group of patients.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Rashid UH: Main idea, data collection.

Khan S: Statistics and bibliography.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.