

Primary thrombophilia in Saudi Arabia

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ABSTRACT

Objective: Venous thromboembolism (VTE) is a common disorder associated with significant mortality and morbidity. Considerable progress has been made in the understanding of the risk factors. Significant portion of patients develop VTE without obvious risk factors. The clinical applications of molecular techniques allowed identification of many important inherited, yet not uncommon risk factors. The aim of our study was to determine whether the activated protein C resistance (APCR)/Factor V Leiden (FVL), and prothrombin mutation as being the most common inherited risk factor for venous thrombosis among Saudi patients attending an anticoagulant clinic.

Methods: One hundred and seventy-nine consecutive patients (74 males, 105 females) accrued in a prospective study with a median age of 42 years (range 17-60 years) have been screened between October 1997 and January 2002 at the King Abdul-Aziz University Hospital (KAUH) and King Fahd Armed Forces Hospital (KFAFH), Jeddah, Kingdom of Saudi Arabia. All patients were Saudis with at least one of the following features: history of recurrent VTE, first episode of unprovoked VTE, thrombosis in unusual site or thrombosis at young age with or without positive family history. Thrombotic workup included protein C, protein S,

antithrombin (AT), APCR, prothrombin mutation, lupus anticoagulant (LA), and anticardiolipin (ACL). Functional assays were carried out in 179 patients. Molecular analysis of both FVL, prothrombin G29210A mutation was performed in 67 patients. All tests were carried out in reference laboratories (Mayo Clinic, United States of America and Bioscientia, Germany).

Results: Protein S deficiency was the most common, identified in 26/179 (14.5%) followed by protein C in 15/179 (8.4%), while AT was not deficient in all 179 tested patients. Activated protein C resistance was present in only 4 patients (2.2%). Two patients were tested positive for prothrombin mutation; one of them was heterozygous for FVL too. Eight percent of the patients had LA, while 4% had ACL antibodies.

Conclusion: Our study shows a different distribution pattern of the underlying thrombophilic state than reported in the western literature. If this holds true in larger trials, this may result in changing our local screening and diagnostic workup in patients with suspected hypercoagulable state.

Saudi Med J 2003; Vol. 24 (6): 614-616

Anticoagulant services are changing in response to the increasing demands on the service, and playing a major role in thrombophilia programs. This explosion is more than likely to be driven by population statistics that show that one out of every 3 individuals in developed countries dies of thrombosis from one of its many forms (stroke, myocardial infarction, pulmonary embolism, and so forth). It is also clear that some individuals harbor one or more abnormalities that predispose them to thrombotic events, the so-called hypercoagulable state. Patients with a tendency to thrombosis are defined as having thrombophilia, and the term inherited

thrombophilia is applied to individuals with predisposing genetic defect. The growing number of genetic abnormalities have been identified that predispose patients to venous thromboembolic disease.¹ Prior to 1993, the diagnosis of a hereditary disorder could be established in approximately 15% of patients under age 50.²⁻³ An extensive range of published literature now exists on the role of heritable thrombophilia.² Antithrombin (AT), protein C and protein S are the major naturally occurring inhibitors of coagulation. Deficiencies of these proteins are relatively uncommon in the general population, the prevalence of

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Received 16th December 2002. Accepted for publication in final form 15th March 2003.

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heterozygous deficiencies is estimated at 10-20%.¹ Activated protein C resistance (APCR) secondary to the Factor V Leiden (FVL) mutation is more common, occurring in 2-15% of Caucasian population and 20-50% of adults with a first episode of venous thromboembolism (VTE).²⁻⁹ Similarly, the prothrombin mutation (PT 20210A), which results in increased levels of prothrombin has a prevalence of approximately 2% in the normal Caucasian population and 6% in unselected adults with VTE.¹⁰ Since there are data suggesting variations in the world distribution of certain hereditary thrombotic conditions.¹¹ We decided to analyze prospectively Saudi patients with clinical features for inherited thrombophilia, in order to assess the prevalence of primary thrombophilic conditions.

Methods. Over a 36-month period all consecutive Saudi patients referred to our Anticoagulant Clinic by the physicians from different departments in both hospitals, King Abdul-Aziz University Hospital and King Fahd Armed Forces Hospital, Jeddah, Kingdom of Saudi Arabia, were prospectively accrued in the study if they had one of the following features: a history of recurrent VTE, first episode of unprovoked VTE; thrombosis in unusual site or thrombosis at a young age with or without positive family history and resistance to conventional antithrombotic therapy.¹² Before any thrombophilic workup, all patients were examined and their medical chart reviewed to ensure no acquired condition can affect the result (for example liver disease, vitamin K deficiency, oral anticoagulant and so forth). The workup investigation performed after 3 months from the VTE. Venipuncture was performed traumatically and the blood sent to the reference laboratory.

Analytical methods. Functional assays were carried out in 179 patients at the Mayo Clinic, United States of America, and a molecular assay in 67 patients at Bioscientia, Germany. The thrombotic workup included AT activity and antigens, protein C antigen and activity protein S antigen total protein S antigen free and APCR phenotype. The 67 patients were screened by molecular analysis for both FVL and PT20210 mutation. All patients were screened for anticardiolipin (ACL) immunoglobulin G and immunoglobulin M isotypes. Lupus anticoagulants (LA), were assessed by multiple tests: activated partial thromboplastin time. Activated partial thromboplastin time mixed studies, Dilute Russell's viper venom time (DRVVT) screen ratio, platelet neutralization procedure (PNP), PNP buffer control, prothrombin time (PT) and thrombin time (TT).

Results. In over 36-month period, 179 consecutive patients (74 males, 105 females) were accrued in the study with a median age of 42 years (range 17-60 years). Protein S deficiency was the most common, identified in 26/179 (14.5%), followed by protein C in 15/179 (8.4%), while AT was not deficient in all 179 tested patients.

Activated protein C resistance was present in only 4 patients (2.2%), 2 of the tested by molecular analysis showed the mutation for FVL. Two patients were tested positive for PT 20210A from the 67 tested; one of them was heterozygous for FVL too. Eight percent of the patients had LA while 4% had ACL antibodies. To summarize the findings identified in this cohort study suggestive of an inherited hypercoagulable protein as follow: protein S deficiency 14.5%, protein C deficiency 8.4%, PT 2.9%, and APCR 2.2%.

Discussion. Venous thromboembolism is now understood to be a complex interaction of genetic and environmental factors leading to thrombosis. In recent years, the ability to diagnose inherited genetic defects and common acquired conditions predisposing to thrombosis has greatly increased. Integrating the various factors to individually assess thrombotic risk still poses a challenging clinical problem that will likely become easier as more data accumulate. When approaching patients with athrombotic diathesis, it is useful to place them in one of 2 major categories. An acquired or secondary state, which consists of a heterogeneous group of disorders being the majority of patients attending the anticoagulant clinic (Table 1). The other group that suggests the presence of an inherited thrombotic disorders, which presented 5% of patients

Table 1 - The most common indication for antithrombotic therapy for patients treated at outpatient anticoagulant clinic.

Patients attending the clinic	%
Valves	20
Ischemic heart disease	15
Myeloproliferative	14
Recurrent deep vein thrombosis/pulmonary embolism	12
Surgery/trauma/unprovoked VTE	8
Congenital heart disease	4
Systemic lupus erythematosus/antiphospholipid antibodies	8
Myeloproliferative disorders/cancer	4
Sickle cell anemia	3
Renal	3
Non cardiac arterial fibrillation	1
Others	3
Inherited thrombophilia	5
VTE - venous thromboembolism	

attending the clinic. Currently thrombophilia screening is usually performed following clinically significant thrombosis. Before performing any specific screening, each patient should be reviewed completely to avoid any acquired disorders for example liver disease. The ideal screening time after passing the acute phase of thrombotic episode and 3 weeks from discontinuation of the oral anticoagulant. Thrombin time (TT) is of additional benefit to the screening, which provides useful information for example normal TT excludes heparin effects and the presence of dysfibrinogenemia and so forth. The clinical application of molecular technique allows identification of many important inherited disorders. Our results confirm the usefulness of thrombophilia workup and confirm the previous study carried out in our department with additional workup and information.¹³ As the ability to assess risk increases, the data can then be translated into tailored treatment regimens until then only general guidelines regarding evaluation and management are available. In the future, it is likely that other prothrombotic condition will be elucidated, adding to the pool of data. The anticoagulant clinic has a major role in thrombophilia programs, which encompasses diagnosis, prevention and treatment. There are 3 major issues in the management of patients with inherited thrombophilia. Primary prophylaxis, secondary prophylaxis and treatment of VTE episodes. The primary prophylaxis may be given a long-term or on demand for special situations that increases the risk of thromboembolism, such as surgery, pregnancy and the puerperium, the long term primary prophylaxis is rarely recommended for asymptomatic individuals, since 49% of VTE episodes in patients with thrombophilia are preceded by a triggering event so primary prophylaxis on demand is recommended. Secondary prophylaxis, once the first thrombotic episode has occurred, a decision has to be made regarding the duration of oral anticoagulation needed preferably lifelong for patients diagnosed as inherited thrombophilia.¹⁴⁻¹⁹

In summary, our study shows different distribution pattern of the underlying thrombophilic state than reported in the western literatures. If this holds true in larger trials, it may result in changing our local screening and diagnostic work in patients with suspected hypercoagulable state.

Acknowledgment. The author acknowledges Dr. Kalida Abu Saud for her help in the anticoagulant clinic and Dr. Hikmat Abdel Razeq, Chairman of Hematology, King Fahd Armed Forces Hospital,

Jeddah, Kingdom of Saudi Arabia, in his cooperative work in the study lately and many thanks to Mrs. Connie Kaba for secretarial help.

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