

# Frequency of Hereditary Thrombophilia: an AKUH experience

S. Khalid, R. Sajid, S. N. Adil, M. Khurshid  
Department of Pathology, The Aga Khan University, Karachi.

## Abstract

**Objective:** To determine the frequency of various causes of hereditary thrombophilia at a referral laboratory and the age and gender distribution.

**Methods:** This is a descriptive study incorporating a retrospective analysis of requests for thrombophilia screening sent to Clinical laboratory, Aga Khan University Hospital from November 1995 to May 2002.

Patients were screened for hereditary causes of thrombophilia including Protein C, Protein S, antithrombin III, Factor V Leiden and homocysteine. Frequency of each disorder; and age and sex distribution was determined.

**Results:** All the patients suspected clinically for thrombophilia were screened. Of the 2825 patients, 70 were diagnosed to have inheritance as a cause of thrombophilia with a frequency of 2.3% for protein C deficiency, 1.4% for protein S deficiency, 1.5% for antithrombin III deficiency, 14.2% for factor V Leiden mutation and 2.0% for homocystenemia.

**Conclusion:** All the causes of hereditary thrombophilia can be diagnosed by relatively simple laboratory methods, however because of the low frequency of these disorders the screening of general population is not indicated in the absence of clinical symptoms. More prospective studies are required to define the occurrence of these disorders and other causes of thrombosis (JPMA 54:427;2004).

## Introduction

Hereditary thrombophilia refers to a group of inherited disorders that is characterized by a defect or deficiency in the natural anticoagulant mechanisms and thus increased predisposition to thromboembolism.<sup>1</sup>

Causes of hereditary thrombophilia include activated protein C resistance (Factor V Leiden), a prothrombin polymorphism that causes elevated plasma prothrombin levels, hyperhomocysteinemia, deficiencies of the anticoagulant factors protein C, protein S and antithrombin III, dysfibrinogenemia and increased levels of factor VIII.<sup>2</sup>

Protein C is a vitamin K dependent serine protease produced in the liver. It is activated by thrombin bound to the endothelium and controls coagulation by inactivating factors Va and VIIIa.<sup>3</sup>

Protein S is a vitamin K dependent glycoprotein produced in the liver. It serves as a cofactor for the cleav-

age and inactivation of factors Va and VIIIa by activated Protein C.<sup>4</sup>

Antithrombin III belongs to a family of serine protease inhibitors (serpins) and is made in the liver. It neutralizes thrombin and other serine proteases of the intrinsic coagulation system (FXa, FIXa, FXIa, and FXIIa).<sup>5</sup>

Factor V is a cofactor for the activation of prothrombin by factor Xa. Arg506 is the site of mutation in factor V Leiden.<sup>6</sup>

Homocysteine is an intermediate in the metabolism of sulfur-containing amino acids, methionine and cysteine.<sup>7</sup> Elevated levels result from disturbances in the homocysteine metabolism.

The majority of the thrombophilic defects either enhance procoagulant reactions or hamper anticoagulant mechanisms and thus cause a prothrombotic state due to hypercoagulability of the blood.<sup>2</sup> Presentation may be during

early childhood or in adulthood. A hereditary thrombophilia should be suspected if the patient is young and has spontaneous thrombosis or recurrent deep vein thrombosis or thrombosis at the unusual sites such as abdominal and cerebral vein thrombosis. With the exception of homocysteinemia, other inherited thrombotic disorders have autosomal dominant inheritance and most patients with these disorders will have appropriate family history.<sup>3</sup>

Laboratory assays are now widely available to identify the great majority of patients with thrombophilia. Laboratory testing is best performed several weeks after completion of a course of oral anticoagulants in patients with thrombosis, to avoid confounding effects of acute thrombosis or, heparin or warfarin therapy on the assay results.<sup>2</sup>

The study aims to find out the frequency of various causes of hereditary thrombophilia at a referral laboratory and to find age and gender distribution of various causes of hereditary thrombophilia.

### Patients and Methods

This is a descriptive case series incorporating a retrospective analysis of patients from all over Pakistan who were suspected to have thrombophilia and referred for screening to clinical Laboratory of the Aga Khan University Hospital from November 1995 to May 2002. These tests were:

- Protein C (Chromogenic method by Dade Behring Berrychrome, Newark, DE, USA)
- Protein S (Clotting method by Dade Behring Berrychrome, Newark, DE, USA)
- Antithrombin III (Chromogenic method by Dade Behring Berrychrome, Newark, DE, USA)
- Factor V Leiden (Clotting method by Dade Behring Berrychrome, Newark, DE, USA)
- Homocysteine (Flourescent particle Immunoassay, Abbott Laboratories)

All the patients were advised to be off warfarin so as to avoid false positive results especially for proteins C and S. Patients were not screened for all causes of hereditary thrombophilia because of physician preference.

### Results

Results are summarized in tables 1 and 2. Total number of patients screened for a cause of thrombophilia was 2825. Out of these, 843 patients were screened for both proteins C and S deficiency, 601 for protein S deficiency, 449 for antithrombin III deficiency, 21 for factor V Leiden mutation and 911 for homocysteinemia. Patients were not screened for all causes of hereditary thrombophilia because of physician preference.

### Discussion

Various studies have been conducted from time to time to determine the frequency of various causes of hereditary thrombophilia. In one study conducted in the Trakya region of Turkey, the prevalence of Antithrombin III, Protein C and Protein S deficiencies was found to be higher than in other reported studies while Factor V Leiden mutation was lower.<sup>8</sup>

In a prospective study on 680 consecutive patients with a history of venous thrombosis, the prevalence of Antithrombin III was 2.8%, Protein C deficiency 2.5%, Protein S deficiency 1.3% and a combined deficiency 0.4%.<sup>9</sup>

In another study by Miljic et al, frequency of Antithrombin III deficiency was 5.8%, Protein C deficiency 4.1% and Protein S deficiency 1.6%.<sup>10</sup>

A prospective study was conducted in Jordan on patients admitted or referred with thromboembolic disease to Jordan University Hospital or to the thrombosis/hemostasis laboratory at the University of Jordan. Total number of patients was 217 and protein C, Protein S and Anti thrombin III deficiency were found to be in 17, 15 and 10 patients respectively. A positive family history was obtained in 65.3% of patients with thrombophilia.<sup>11</sup>

In another study conducted in Israel, 107 unrelated patients were evaluated over four years to estimate the relative frequency of hereditary disorders leading to thrombophilia and they were found to be 5.6%, 2.8% and 7.5% respectively in Protein C, Protein S and Antithrombin III deficiency.<sup>12</sup>

In a study conducted in Taiwan, 85 consecutive and unrelated patients with otherwise unexplained thrombophilia were studied. A relatively higher prevalence of Anti thrombin III, Protein C and Protein S, but no factor V Leiden mutation was found in Chinese patients in Taiwan compared to that in western countries.<sup>13</sup>

In a local study conducted by Armed Forces Institute of Pathology, Antithrombin III levels were studied in 32 patients with median age of 29.1 years. Overall frequency of Antithrombin III deficiency in young adults was 6.2% and was confined to patients with venous thromboembolic disease.<sup>14</sup>

All the causes of hereditary thrombophilia reported in literature are also seen in our population. However, after literature review, it can be seen that the deficiencies of Protein C, Protein S and Antithrombin III are more common. But in our study, due to the unequal number of requests which we received for thrombophilia screening, it is not clearly defined that which disorders are more common.

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On the other hand, age and gender distribution are not taken into consideration in other studies but it was one of our objective. Although, these disorders can present in all age groups, it was found that majority of the patients presented during 35 to 45 years of age.

All the causes of hereditary thrombophilias can be diagnosed by relatively simple laboratory methods, however because of the low frequency of these disorders the screening of general population is not indicated in the absence of clinical symptoms. More prospective studies are required to define the occurrence of these disorders and

other causes of thrombosis.

The tests should be carried out if the patient is young and has spontaneous thrombosis or recurrent deep vein thrombosis or thrombosis at unusual sites such as abdominal and cerebral vein thrombosis. The clinical awareness of these disorders along with the factor of consanguineous marriages and availability of screening kits may show an increased incidence in our population.

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The collaboration of WHO with the Government of