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original article

Epidemiological Aspects and Genetic Study of Hereditary Thrombophilia in Egyptian Population

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Abstract:

Background: Thrombophilia are hereditary or acquired conditions which can increase the risk of venous or arterial thrombosis. As the etiology of thrombosis is multifactorial, the presence of a thrombophilia defect is only one of many elements that determine risk. Therefore, the utility of testing for thrombophilia to inform prevention and treatment decisions- is controversial. The aim of this work was to study epidemiological aspects and genetic mutation of inherited thrombophilia in Egyptian patients. **Methods:** The present study represents a case control study and was approved by the ethics committee on research involving human subjects of Benha Faculty of Medicine. Written informed consents were obtained from all participants. It was conducted on 64 cases with unexplained deep venous thrombosis, any site all over the body, with age ranged from 16 to 40 years. Fifty-nine points, four percent of them- were males, and forty point six percent- were females. **Results:** Of all these defects in 56 cases of our study; MTHFR C677T mutation was the most frequent defect, then MTHFR A1298C, FVL, FXIII V34L, beta fibrinogen and prothrombin G21211. **Conclusion:** We found that MTHFR C677T mutation is important risk factor for thrombosis in Egyptian patients. The presence of this polymorphism can increase the risk of thrombosis. Patients with thrombosis- at any site of their body- have a significantly higher prevalence of MTHFR C677T mutation, FVL, FXIII V34L, beta fibrinogen and prothrombin G21211, compared to healthy controls. Of all these defects; MTHFR C677T mutation was the most frequent defect.

Key words: Epidemiological aspects and genetic; hereditary; thrombophilia; Egyptian population.

Introduction

Thrombophilia is a hypercoagulable state that predisposes to thrombosis. It is manifested by inappropriate blood clot formation- a multifactorial condition- that could arise from genetic, acquired factors or a combination of both. Thrombotic events are steadily recognized as an important source of morbidity and mortality [(1).]

Thrombophilia are hereditary or acquired conditions which can increase the risk of venous or arterial thrombosis. As the etiology of thrombosis is multifactorial, the presence of a thrombophilia defect is only one of many elements that determine risk. Therefore, the utility of testing for thrombophilia to inform prevention and treatment decisions is controversial [(2).]

Acquired thrombophilia is not a disease per se, but may be associated with a disease (e.g., cancer), drug exposure (e.g.**,** oral contraceptives) or condition (e.g.**,** pregnancy or postpartum, secondary thrombophilia), and thrombophilia may be inherited [(3).]

This concept is important because disease susceptibility does not imply an absolute requirement for primary or secondary prevention, or for treatment**.** Most persons with a thrombophilia do not develop thrombosis. Thus, thrombophilia must be considered in the context of other risk factors for incident thrombosis, or predictors of recurrent thrombosis, when estimating the need for primary or secondary prophylaxis**,** respectively [(3).]

Hereditary'' or ''inherited'' thrombophilia has most commonly been applied to conditions in which a genetic mutation affects the amount or function of a protein in the coagulation system. Loss of function mutations include those affecting antithrombin (AT), protein C (PC) and protein S (PS). Gain of function mutations include the factor V Leiden (FVL) and the prothrombin gene 20210 A/G (PGM) mutations [(2).]

The aim of this work was to study epidemiological aspects and genetic mutation of inherited thrombophilia in Egyptian patients.

Patients and Methods

The study was carried out in haemato-oncology unit, Internal medicine department, Benha University Hospital, from May 2021 to May 2022 and arranged to receive International Review Board (IRB) approval from Benha IRB unit {M.S.13.6.2021}. This prospective study was carried on 64 young Egyptian patients with unexplained deep venous thrombosis, any site all over the body.

Inclusion criteria:

- Age <40 years
- Unprovoked deep venous thrombosis.

Exclusion criteria:

- Any patient with risk factor for deep venous thrombosis.
- Malignancy
- Elderly patients
- Pregnancy
- Antiphospholipid syndrome
- Vasculitis

Method:

- Complete history taking.
- Thorough physical examination.
- Doppler ultrasound for detection of deep venous thrombosis
- PCR for genetic mutation hereditary thrombophilia

Statistical analysis

The collected data was revised, coded, tabulated using Statistical package for Social Science (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

Normality of data

- Shapiro test was done to test the normality of data distribution.

Descriptive statistics:

- Mean, Standard deviation (± SD), minimum and maximum- were used to describe normally distributed numerical data. While median, minimum and

maximum- were used to describe non normally distributed numerical data.

- Frequency and percentage were used to describe non-numerical data.

Analytical statistics:

- **Student T** Test was used to assess the statistical significance of the difference between two study group means.
- **Chi-Square test** was used to examine the relationship between two qualitative variables.

Probability of results

- All reported p values were two-tailed and $p < 0.05$ was considered to be significant.

Results:

Table (1). Demographic data and family history among the included cases.

			Thrombophilia n=64	
Age (years)		**Mean ±SD (min-max)**	30±6.8 (16-40)	
Sex	**Male**	**N, %**	38	59.4%
	Female	**N, %**	26	40.6%
Family History	**Negative**	**N, %**	36	56.3%
	Positive	**N, %**	28	43.8%

The mean (±SD)age of the studied cases was 30 (±6.8), ranged from 16 to 40 years, 38 cases were males (59.4%) and 26 cases were females (40.6%). Out of them,36 cases had negative family history of DVT (56.3%) and 28 cases had positive family history (43.8%).

Table (2). Clinical presentations among the included patients.

	Thrombophilia n=64	
	Count	**%**
Deep vein thrombosis	24	37.5%
Portal vein thrombosis	12	18.8%
Pulmonary embolism	12	18.8%
Sagittal thrombosis	8	12.5%
Central Retinal vein thrombosis	4	6.2%
Mesenteric vascular occlusion	2	3.1%
Cerebral sinus thrombosis	2	3.1%

Regarding the clinical presentation among the studied cases, 24 cases had Deep vein thrombosis (37.5%), 12 cases had Portal vein thrombosis (18.8%), 12 cases had Pulmonary embolism (18.8%), 8 cases had Sagittal thrombosis (12.5%), 4 case had Central Retinal vein thrombosis (6.2%), (3.1%), 2 case had Mesenteric vascular occlusion (3.1%) and 2 case had Cerebral sinus thrombosis (3.1%).

Table (3). Clinical presentations Laboratory finding among the included patients.

	Thrombophilia n=64	
	mean±SD	**min-max**
Protein C	97±37.8	21-200
Protein S	86±32.1	29-160
Anti thrombin111	102±32.2	29-202

Regarding the laboratory finding among our cases, mean Protein C was 97 ranged from 21 to 200; mean Protein S was 86 ranged from 29 to 160, and mean Anti thrombin111 was102, ranged from 29 to 202.

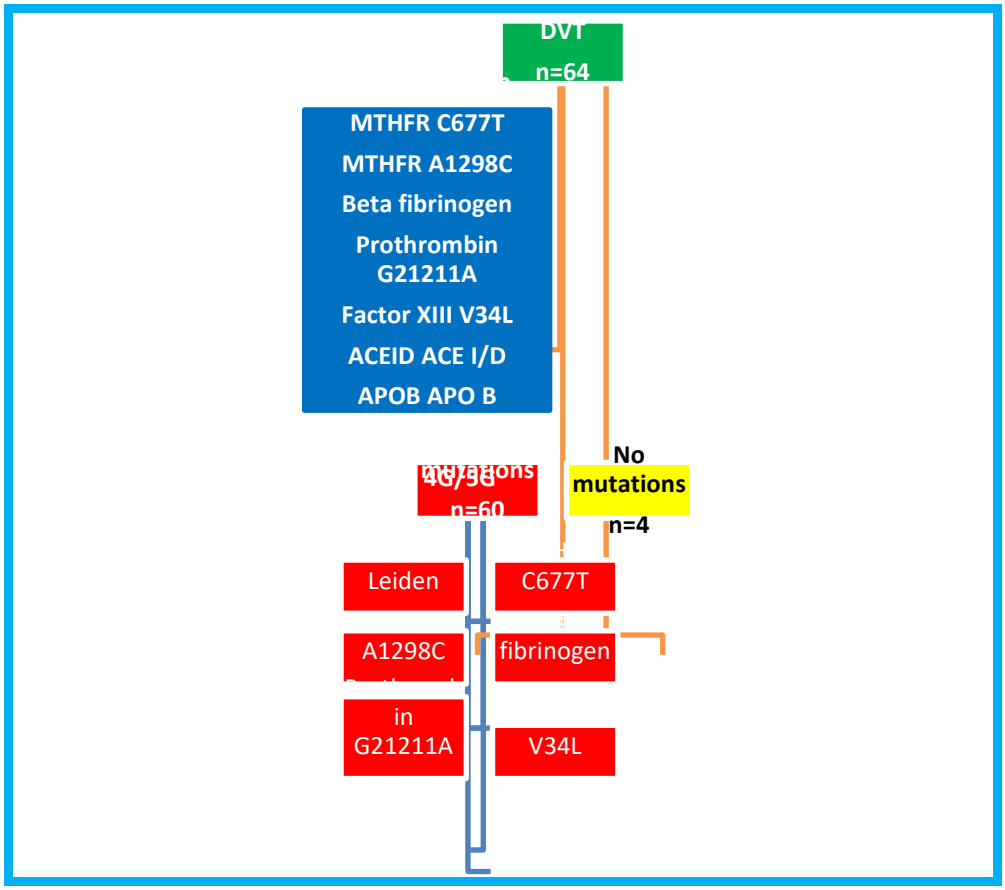

Figure (1). PCR results for genetic mutation of hereditary thrombophilia

The current patients were subjected to thrombophilia screening panel, out of them 60 cases had mutations and only 4 cases had no mutations, 42 had MTHFR C677T, 34 had MTHFR A1298C, 30 had FVL, 8 cases had FXIII V34L, 4 had beta fibrinogen and 4 had prothrombin G21211A

Table (4). PCR results for genetic mutation of hereditary thrombophilia.

	Thrombophilia n=64							
	Normal		Heterozygous		Mutated		Positive	
	Count	%	Count	%	Count	%	Count	%
Factor V Leiden	34	53.1%	22	34.4%	8	12.5%	30	46.9%
MTHFR C677T	22	34.4%	38	59.4%	4	6.3%	42	65.7%
MTHFR A1298C	30	46.9%	30	46.9%	4	6.3%	34	53.2%
Beta fibrinogen	60	93.8%	4	6.3%	0	0%	4	6.3%
Prothrombin G21211A	60	93.8%	4	6.3%	0	0%	4	6.3%
Factor XIII V34L	56	87.5%	8	12.5%	0	0%	8	12.5%
ACEID ACE I/D	64	100%	0	0%	0	0%	0	0%
APOB APO B	64	100%	0	0%	0	0%	0	0%
APOE APO E	64	100%	0	0%	0	0%	0	0%
PAI-1 4G/5G	64	100%	0	0%	0	0%	0	0%

Positive= Heterozygous+ Mutated

It is noticed that the highest prevalence of positive mutation among the current cohort was related to MTHFR C677T (56.7%), followed by MTHFR A1298C (53.2%), then FVL (46.9%).

Regarding the PCR results for genetic mutation of hereditary thrombophilia, the following results were detected; normal FVL (53.1%), heterozygous (34.4%), mutated (12.5%), i.e. positive factor (46.9%).
Regarding MTHFR C677T, normal (34.4%), heterozygous (59.4%), mutated (6.3%); i.e. positive factor (65.7%).
Regarding MTHFR A1298C, normal (46.9%), heterozygous (46.9%), mutated (6.3%); i.e. positive factor (53.2%).
Regarding Beta fibrinogen, normal (93.8%), heterozygous (6.3%).
Regarding Prothrombin G21211A, normal (93.8%), heterozygous (6.3%).
Regarding Factor XIII V34L, normal (87.5%), heterozygous (12.5%).
All studied cases had normal ACEID ACE I/D, APOB APO B, APOB APO E, PAI-1 4G/5G.

Table (5). PC, PS, and ATIII levels among different detected mutations.

	Positive mutations				
	factor V Leiden n=30 mean± SD	**MTHFR C677T n=42 mean± SD**	**MTHFR A1298C n=42 mean± SD**	**Beta fibrinogen n=4 mean± SD**	**Factor XIII V34L n=8 mean± SD**
Protein C	106±41.2	103±35.2	100±25.6	120±17.7	120±17.3
Protein S	86±23.2	92±34.5	90±28.8	102±15.3	102±15.6
Anti thrombin111	110±35.1	108±29.1	103±17.2	82±26.9	82±26.3

Lowest PC level was associated with MTHFR A1298C, followed by C677T, then FVL mutations.
Lowest PS level was associated with FVL, followed by MTHFR A1298C, then C677T mutations.
Highest AT III was associated with FVL, followed by MTHFR C677T, then A1298C mutations.

Table (6). Clinical presentations among studied mutations.

	Positive mutations									
	FVL n=30		**MTHFR C677T n=42**		**MTHFR A1298C n=42**		**Beta fibrinogen n=4**		**Factor XIII V34L n=8**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Deep vein thrombosis	16	25.0%	16	25.0%	8	12.5%	2	3.1%	2	3.1%
Portal vein thrombosis	8	12.5%	10	15.6%	6	9.4%	0	0.0%	0	0.0%
Pulmonary embolism	4	6.3%	6	9.4%	4	6.3%	0	0.0%	0	0.0%
sagittal thrombosis	0	0.0%	6	9.4%	8	12.5%	2	3.1%	2	3.1%
Central Retinal vein thrombosis	0	0.0%	0	0.0%	4	6.2%	0	0.0%	0	0.0%
Mesenteric vascular occlusion	2	3.1%	0	0.0%	2	3.1%	0	0.0%	0	0.0%
Cerebral sinus thrombosis	0	0.0%	2	3.1%	2	3.1%	0	0.0%	0	0.0%

Percentages are calculated out of all studied cases (n=64).
Among those with DVT, mutations detected were FVL (25%), MTHFR C677T (25%), A1298C (12.5%), β fibrinogen (3.1%) FXIII V34L (3.1%).
Among those with PVT, mutations detected were FVL (12.5%), MTHFR C677T (16.5%), A1298C (9.4) %.
Among those with PE, mutations detected were FVL (6.3%), MTHFR C677T (9.4%), A1298C (6.3%).

Among those with ST, mutations detected MTHFR C677T (9.4%), A1298C (12.5%), β fibrinogen (3.1%) FXIII V34L (3.1%).
Among those with CRVT, mutations detected MTHFR A1298C (6.2%).
Among those with ST, mutations detected were MTHFR C677T (9.4%), A1298C (12.5%), β fibrinogen (3.1%) FXIII V34L (3.1%).
Among those with MVO, mutations detected FVL were (3.1%), MTHFR A1298C (3.1%).
Among those with CST, mutations detected were MTHFR C677T (3.1%), A1298C (3.1%).

Discussion

In our study, it was interesting to find out that 43.8% of the cases in our study has positive family history of DVT. A familial component of venous thrombosis was first fully recognized in the 1960s when reduced levels of AT- were shown to be associated with recurrent thrombosis in a family [(4).]
Since this discovery, multiple studies have shown almost 250 different mutations for AT deficiency and the risks associated with this disorder [(5).]
The study by Broekmans [(6)] of three Dutch families provided further understanding of this deficiency and confirmed the autosomal dominant inheritance pattern. That study of protein C demonstrated that inherited thrombophilia was a polygenic disorder with variable expressivity.
This was followed a few years later with the discovery of an inherited deficiency of the co-factor for protein C, protein S. All three of these proteins, AT, protein C and protein S- play a role in the downregulation of coagulation. Deficiencies of these proteins result in an increased generation of thrombin and a predisposition to thrombosis [(7).]
Khan [(8)] described a large family from southern Sweden who demonstrated thrombosis in males and females throughout several generations and showed an autosomal dominant pattern of inheritance.
Studies have been done in various populations to understand the inheritance patterns and risks for individuals with an inherited thrombophilia. Familial thrombosis was originally considered an autosomal dominant disorder with varying expression and penetrance. However, more recent studies suggest that congenital thrombophilia may in fact be the result of the combination of two or more gene defects in a family [(5).]
However, Cohoon [(3)] said that the family history of VTE is not a predictor of VTE recurrence and should not influence the decision regarding secondary prophylaxis.
The current study showed that the mean Protein C was 97 ranged from 21 to 200; mean Protein S was 86 ranged from 29 to 160, and mean Anti thrombin111 was102, ranged from 29 to 202.
Usually, PC deficiency is thought to be transmitted as an autosomal dominant trait with a high degree of penetrance, but in families with individuals with complete deficiency, the mode of inheritance has been classified as autosomal recessive. The prevalence of PC deficiency is 0.2% to 0.4% in the general population and 3.0% in unselected VTE patients [(9).]
Heterozygotes exhibit roughly ten times the normal risk of thrombosis. Thrombosis associated with the deficiency state generally requires a longer period of anticoagulation (12–24 months), but not necessarily life-long anticoagulation. The disorder is somewhat rare, with a prevalence in the population of only 0.2–0.4%. Prevalence observed in patients with venous thrombosis is 3–5% (10).
Khan [(5)] said in their study that protein C deficiency is less common than either the factor V Leiden or the prothrombin G20210A gene mutation with prevalence in Caucasians estimated to be 0.2–0.5%.
That has showed that family members who are Protein C deficient are at an 8–10-fold increased risk of venous thrombosis, and,

by age 40, 50% or more will have experienced a thrombotic event [11].

That has concluded that the median age at onset for a thrombotic event and the risk of thrombosis is similar in both protein C deficiency and factor V Leiden (APC resistance). Approximately 60 percent of affected individuals develop recurrent venous thrombosis and about 40 percent- have signs of pulmonary embolism [12].

Laboratory diagnosis of inherited protein C deficiency is complicated by several factors that can influence the measured level of the protein. Pregnancy and the use of oral contraceptives can lead to increased levels. Levels can be decreased in the setting of an acute thrombus, liver disease, renal disease, heavy smoking and disseminated intravascular coagulation [13].

As protein C is a vitamin-K-dependent factor, anticoagulation with warfarin or vitamin-K-deficiency will also cause decreased levels, such that a deficiency state cannot be accurately diagnosed within 2 weeks of receiving oral anticoagulation [14].

Despite these limitations, and the rarity of the disorder, testing for protein C deficiency is useful. As is the case in antithrombin deficiency, establishment of the diagnosis may change therapy, leading to more prolonged anticoagulation and the use of protein C concentrates when necessary. Most sources recommend performing a functional clotting-based test instead of an immunological assay. Because of the large number of known mutations, genetic analysis is not a practical approach for diagnosis [14].

Protein S serves as a cofactor for activated protein C. It was originally discovered and purified in Seattle, leading to the designation protein S. In a Spanish study of 2132 consecutive unselected patients with venous thromboembolism, 7.3 percent had protein S deficiency [15].

Inherited PS deficiency is transmitted as an autosomal dominant trait. Its prevalence of the trait in the general population is estimated at 0.03–0.13%. Among individuals with a thromboembolic event, prevalence is 1–5% [9].

Other studies, estimated the lifetime probability of developing thrombosis among carriers of protein S deficiency- was 8.5 times higher compared to those with no defect [16].

That was studied 122 members in a family, with 44 of the members previously characterized for the specific gene defect in protein S. The study showed little thrombotic risk before the age of 15 years. On the other hand, the likelihood of being free of thrombosis by age 30- was only 50 percent compared to 97 percent in normal family members. The odds ratio for thrombosis in affected subjects was 11.5, and the study showed that measurement of free protein S antigen levels was predictive of the mutation and deficiency [17].

A UK based family study with 28 index patients with protein S deficiency, first degree relatives with the PROS1 gene defect- had a five-fold higher risk of thrombosis than those with a normal gene and no other apparent thrombophilia [18].

According to a meta-analysis of observational studies by Di Minno et al., the relative risk of a first episode of VTE associated with PS deficiency was 5 and the relative risk of recurrence was 2.5 (but not significant) [19].

Several studies have shown that PS-inherited deficiencies associated with an increased risk of thrombosis are those for which plasma-free PS is greatly reduced, with a risk threshold (30-40%) lower than the lower limit of the reference values [20].

The majority of AT-deficient patients identified in studies did not have a personal or familial history of thrombosis. Among patients with a first thrombotic event, the prevalence of hereditary AT deficiency- is approximately 0.5 to 1 percent, being less common than factor V Leiden, the prothrombin gene mutation, or protein S/protein C deficiency [5].

However, in a study they found that the antithrombin deficiency is probably the most severe of the inherited thrombophilia,

imparting up to a 20-fold increased risk for thrombosis compared to those who do not carry the mutation. Fortunately, the diagnosis is also quite rare, with an estimated prevalence of only 0.02% in the general population. Prevalence among patients presenting with venous thromboembolic disease is estimated at 1–3% [21].

Despite the low likelihood of diagnosing antithrombin deficiency in a patient presenting with thrombosis, laboratory evaluation of antithrombin activity is probably warranted owing to its impact on therapeutic considerations. As mentioned above, a diagnosis of symptomatic antithrombin deficiency usually leads to life-long anticoagulation in the absence of specific contraindications. In addition, the deficiency is one of the few inherited thrombophilia that can be treated with replacement therapy. Antithrombin concentrates can be very useful as prophylaxis in situations where there is a high risk of bleeding- such as surgery or delivery- or in cases of thrombosis refractory to heparin [22].

That was study showed that homozygous children of consanguineous parents who were asymptomatic carriers developed severe venous or arterial thrombosis in association with plasma AT-heparin cofactor levels below 10 percent of normal [23].

The lifetime probability of developing thrombosis compared to those with no defect was 8.5 times higher for carriers of protein S deficiency, 8.1 for type I antithrombin deficiency, 7.3 for protein C deficiency, and 2.2 for factor V Leiden [16].

The current study showed that 60 cases of the studied patients which subjected to thrombophilia screening panel, had mutations and only 4 cases had no mutations, 42 had MTHFR C677T, 34 had MTHFR A1298C, 30 had FVL, 8 cases had FXIII V34L, 4 had beta fibrinogen and 4 had prothrombin G21211A.

Published a study in 1997 based on 4047 American men and women participating in the Physician's Health Study and the Women's Health Study. The study found a 12 percent incidence of heterozygosity for the factor V Leiden mutation in patients with a first confirmed deep vein DVT or pulmonary embolism compared with 6 percent in controls [24].

That found the prevalence of heterozygosity for the factor V Leiden mutation in Europeans, Israeli, Arab, Canadian and Indian populations- ranges from 1 to 8.5 percent with most European studies reporting overall rates between 5 and 8 percent but the prevalence is highest in Greece, Sweden, and Lebanon where it approximates 15 percent in some areas. On the other hand, the mutation is apparently not present in African Blacks, Chinese, or Japanese populations. Although possibly influenced by a selection bias, the lifetime probability of developing thrombosis is considerably less in heterozygotes with the factor V Leiden mutation than in patients with the less common inherited thrombophilia's [25].

Homocysteine is an amino acid that is produced in the body by the metabolism of methionine. Homocysteine in turn is metabolized by two main pathways. The first pathway involves the enzyme cystathionine b-synthase (CBS) and requires vitamin B6. The second pathway involves the enzyme methionine synthase and requires both vitamin B12 and N5-methyltetrahydrofolate, a metabolite of folic acid produced by the enzyme methylene tetrahydrofolate reductase (MTHFR). Nonfunctional mutations in the above genes can be inherited as rare autosomal recessive traits, leading to severe hyper-homocysteinaemia, characterized by several clinical features including venous thrombosis [18].

Homozygosity for the thermolabile form of MTHFR alone does not result in an increased risk in the absence of high homocysteine levels. Also, of interest is the fact that supplementation with vitamin B6, B12 and folate- can often reduce homocysteine levels to normal, but this

therapy has not yet been shown to result in a decreased risk of thrombosis [18].

However, it was said in their study that genetic testing for the thermolabile variant of MTHFR has no role in the diagnosis of hyper-homocysteinaemia, as the inherited trait alone has not been shown to be a significant independent risk factor for venous thrombosis [26].

A study in Italy in 2000, demonstrated that missense mutations in the beta-fibrinogen gene could cause congenital afibrinogenemia by impairing fibrinogen secretion. However, the exact mechanism of how abnormal fibrin results in thrombosis is yet to be elucidated [27].

In the current study, it was interested to notice that the highest prevalence of positive mutation among the current cohort was related to MTHFR C677T (65.7%), followed by MTHFR A1298C (53.2%), then FVL (46.9%).

These results coincide with the study conducted on a Lebanese family which found a minor correlation was documented for MTHFR C677T and VTE unless additional risk factors are present [1].

In our study, we found that Lowest PC level was associated with MTHFR A1298C, followed by C677T, then FVL mutations. Lowest PS level was associated with FVL, followed by MTHFR A1298C, then C677T mutations. Highest AT III was associated with FVL, followed by MTHFR C677T, then A1298C mutations.

In normal subjects, activated protein C exerts its anticoagulant affect by proteolytically degrading the procoagulant factors Va and VIIIa. The factor V Leiden mutation is a single base transition in the gene that leads to a substitution of arginine for glutamine at position 506 in the synthesized protein. The defective factor V produced is resistant to cleavage by activated protein C, ultimately resulting in the production of higher levels of thrombin and a higher likelihood of thrombosis. The factor V Leiden mutation itself accounts for about 95% of cases of activated protein C resistance. Of patients presenting with thromboembolic disease, 10–50% will be found to carry the trait [28].

Conclusion:

We found that MTHFR C677T mutation is important risk factor for thrombosis in Egyptian patients. The presence of this polymorphism can increase the risk of thrombosis. Patients with thrombosis- at any site of their body- have a significantly higher prevalence of MTHFR C677T mutation, FVL, FXIII V34L, beta fibrinogen and prothrombin G21211- compared to healthy controls. Of all these defects; MTHFR C677T mutation was the most frequent defect.

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