Thrombophilia in Patients with Cryptogenic Stroke

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ABSTRACT

Introduction*: Cryptogenic stroke means stroke with unexplained aetiology, in manycases the cause of stroke remains undetermined in spite of full investigations. Those patients are thought to have hypercoagulable state, the purpose of study is to unmask some of the pathogenic mechanisms underlying cryptogenic stroke through assessment of some genetic disorders including C677T mutation in methylenetetrahydrofolate reductase gene and activated protein C (APC) resistance, and the role of thrombin anti-thrombin complex concentration in plasma as indicator of hypercoagulable state.* ***Subjects and Methods:*** *The study is case-control study that was conducted on 20 Egyptian patients who were classified into 2 groups; group I includes 10 patients with cryptogenic stroke who are less than 50 years and group II that includes 10 age and sex-matched patients with non-cryptogenic stroke. They were subjected to a panel of investigations including all routine labs and imaging studies in order to exclude any conventional risk factors for stroke in group I patients and to determine the risk factors for stroke in group II, then both groups are investigated for C677T mutation in methylenetetrahydrofolate reductase gene, activated protein C (APC) resistance and thrombin anti-thrombin complex concentration in plasma.* ***Results:*** *revealed no statistical significant difference was found between the two groups as regard C677T mutation in methylenetetrahydrofolate reductase gene, activated protein C (APC) resistance, and thrombin anti-thrombin complex concentration(TAT) in plasma (P value >0.05), TAT level was positively correlated with clinical severity in non-cryptogenic stroke (P value <0.05).* ***Conclusion****: C677T mutation in methylenetetrahydrofolate reductase gene, activated protein C (APC) resistance and thrombin anti-thrombin complex concentration in plasma are not independent risk factors for cryptogenic stroke, thrombin anti-thrombin complex concentration (TAT) could be used as indicator of clinical severity and prognosis in patients with non-cryptogenic stroke.* **(Egypt J. Neurol. Psychiat. Neurosurg., 2008, 45(2): 549-560)**

INTRODUCTION

Stroke is the most common life-threatening neurological disease and the third most common cause of death world-wide[1].

Approximately 40% of cerebral infarctions can not be classified as strokes of determined cause despite a complete diagnostic work-up and can be referred to as cryptogenic strokes[2].

In the past several years, however, tremendous progress has been made in our understanding of the heterogeneity of thrombosis risk in the general population and in our ability to identify a specific, inherited predisposing factor in patients with thrombosis. The most dramatic advance was the discovery of resistance to activated protein C (APC)[3].

The phenomenon of activated protein C resistance (APCr) was first reported by Dahlback et al. in 1993[4]. Clinically this results in an increased risk of thrombosis. Most cases of APC resistance are associated with a single point mutation in the factor V gene (Leiden mutation)[3].

In addition to the factor V gene (Leiden mutation), poly-morphism of angiotensin I-converting enzyme (ACE) gene, prothrombin gene, 5, 10-methylenetetrahydrofolate reductase gene (MTHFR), endothelial cell nitric oxide synthase (ecNOS) gene, tissue plasminogen activator (tPA) gene, plasminogen activator inhibitor-1 (PAI-1) gene, and HaeIII polymorphisms of the ß-fibrinogen gene. Each of these genes is important in maintaining vascular tone and/or hemostasis and hence may be important in the etiology of thrombotic disease and cryptogenic stroke[5].

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Methylenetetrahydrofolate reductase (MTHFR) acts at a critical metabolic juncture in homocysteine metabolism through the regulation of cellular methylation reactions, catalyzing the conversion of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the methyl donor for the remethylation of homocysteine to methionine[6]

The C to T missense mutation in the MTHFR gene (677C→T) produces a thermolabile form of the enzyme, reduces enzyme activity and results in increased plasma homocysteine that may lead to vascular damage and consequently ischaemic stroke[6].

Thrombin Anti-Thrombin Complex (TAT) produced during the inactivation of thrombin, the central enzyme of the hemostasis system, when it forms a complex with antithrombin. So it is considered as an indirect measure of thrombin formation, i.e. the in vivo activation of coagulation. In other words, it could be regarded as an indicator of the presence of hypercoagulable state[7].

SUBJECTS AND METHODS

Subjects:

This case-control study was conducted on 20 Egyptian patients presenting with cerebrovascular ischaemic stroke to Neurology out-patient clinic, Kasr El-Aini Hospital ,They were enrolled from April 2005 till May 2006.They were 12 male patients (60%) and 8 female patients (40%), their age ranges from 18 to 49 years. Those patients were divided into 2 groups:

* **Group I:** Patients with cerebrovascular ischaemic stroke of undetermined aetiology (cryptogenic stroke).
* **Group II** (control group): Patients with cerebrovascular ischaemic stroke of determined aetiology (non-cryptogenic stroke).

Group I: This group consisted of 10 patients (6 males and 4 females).

Inclusion criteria:

1. Patients with ischemic cerebrovascular stroke (whether recent or old).
2. Age below 50 years.

Exclusion criteria:

1. Patients with hemorrhagic cerebrovascular accident as evident by CT or MRI brain.
2. Patients with evident cardiac source of emboli (by TTE or TEE).
3. Patients having significant carotid atherosclerotic plaque.
4. Patients with evident vascular risk factors Hypertension, diabetes,dyslipidemia or hyperuricaemia.
5. Patients with evidence of vasculitis e.g. positive ANA, ANCA.
6. Patients with blood disease e.g. Polycythemia, Essential thrombocytosis, Leukemia.
7. Patients with other causes of hypercoagulable state e.g. pregnancy, patients receiving oral contraceptive pills, malignancy etc…
8. Patients on anticoagulation in order not to interfere with results of different hemostatic parameters.

Group II (control group):

This group consisted of 10 age and sex-matched patients (6 males and 4 females) with cerebrovascular ischaemic stroke of determined aetiology (non-cryptogenic stroke) e.g. Diabetic, hypertensive etc…

Methods:

The patients were subjected to the following battery of assessment:

I) Clinical evaluation:

1. History taking from patients or near relatives.
2. Examination: General medical examination including vital signs especially blood pressure and pulse, cardiological assessment and chest examination, Neurovascular examination & Neurological examination.
3. Assessment of functional outcome: All patients were assessed by the National Institute of Health stroke scale (NIHSS) upon their entry in the study ,The NIHSS score can be classified into mild stroke 0-5, moderate stroke 6-10**,** moderately severe stroke 11-15**,** severe stroke 16-22 & very severe stroke >22 [8].

II) Laboratory Work-up: including complete blood count (CBC), erythrocyte sedimentation rate (ESR), fasting (FBS) and 2 hours post-prandial blood sugar (PPBS) levels. Lipid profile, serum uric acid, liver and kidney functions, serum electrolytes, protein C, protein S, antithrombin III, anti-cardiolipin antibodies (IgG and IgM), auto-immune profile including ANA and ANCA, cryoglobulins, lupus anticoagulant, complement C3, C4 level, serum homocysteine level

- **MTHFR (methylenetetrahydrofolate reductase enzyme) gene mutation** :

Genomic DNA from each patient was extracted from peripheral blood leucocytes according to standard methods with QIA amb DNA Blood Mini Kit (QIA GEN, valen-tia, ca.).

The MTHFR gene mutations, 677C-T was characterized by PCR-ARMS. Briefly, 500 ng of genomic DNA was incubated in a total reaction volume of 50 µl containing final concentrations of 500 nM of the forward and the reverse primers, 200 µM each dNTP, 10 mM Tris-HCl pH 8.3, 50 mM KCl, 2 mM MgCl2, 0.05% detergent and 1 unit Taq DNA polymerase (Life Technologies).

PCR conditions were optimized for the Omnigene (Hybaid) apparatus and included denaturation at 94 °C, annealing at 70 °C for C677T and extension at 72 °C.

The C677T variant creates a HinfI site, after restriction enzyme digestion, PCR products were evaluated by gel electrophoresis analysis [9,10].

Activated protein C:

Biochemistry:

Activated protein C is glycoprotein composed of a heavy chain and a light chain held together by a disulphide bond. Its molecular weight is about is 61.000 and optimal ph is 8.0-9.0. Its natural substrates are the activated forms of the coagulation factors V and VIII.

Principle:

The determination of APC-resistance of a plasma sample is based on the prolongation of its activated partial thromboplastin time (APPT) in the presence of APC, its APPT without APC being normal[4].

Application: Determination of the sensitivity to Activated protein C:

Intended use: for the detection of a drop in the sensitivity to the anticoagulant action for activated protein C Which is referred to as APC-resistance. This drop in sensitivity is associated with the presence of an abnormal form of factor Va called factor V Leiden (mutation Arg 506→Gln)[11]. Patients having this abnormal condition is prone to thrombosis[4].

- **Thrombin-Antithrombin complex concentration (TAT)**:

Enzygnost TAT micro is a sandwich enzyme immunoassay for the in vitro determination of human thrombin antithrombin complex (TAT), during the first incubation step the TAT in the sample binds to the antibodies against thrombin which are attached to the surface of microtitration plate. Unbound constituents are then removed by washing and, in a second reaction, peroxidase-conjugated antibodies to human anti-thrombin III are bound to the free anti-thrombin III determinants.

The excess enzyme-conjugated antibodies are removed by washing. The bound enzyme activity is then determined.

The enzymatic reaction between hydrogen peroxide and chromogen is terminated by the addition of diluted sulphuric acid. The resulting colour intensity, which is proportional to the concentration of TAT, is determined photometrically. The concentration range of 2 to 60 ug/L is converted by the standards contained in the kit[7].

III) Imaging:

1. **Computed tomography**:

CT was done for all patients included in this study, CT brain was performed with the objective of obtaining information regarding presence or absence of cerebral infarction, Cerebral infarction has been classified according to size into small vessel disease and large vessel disease. Hemorrhagic stroke cases were excluded after the CT was preformed. Some cases that presented during the acute stage (within first 72 hours of onset) the CT showed no abnormality, so a follow up CT was preformed for these cases after 72 hours. Few patients had MRI brain preformed initially or as follow up.

2. **Duplex**:
   All patients were subjected to B-mode and colour-coded duplex sonography of the extracranial and vertebrobasilar arteries. Carotid and Vertebrobasilar risk factor was identified as follows:
   a- Less than 50% stenosis carries a minor risk
   b- Equal to or more than 50% stenosis carries a high risk[12].
3. **Echocardiography**:
   All patients were subjected to transthoracic echocardiography & transesophageal echocardiography. Patients with abnormal echocardiography e.g. RHD, atrial septal abnormalities, cardiomyopathy etc) were excluded.

IV) Statistical analysis:

The data were coded and entered using the statistical package SPSS version 11.01. The data were summarized using the mean and standard deviation (S.D.) for quantitative data and the frequency distribution for qualitative data.

The student's t-test was used to assess statistical differences between two groups of quantitative data. Mann-Whitney U test was used for comparison when data was not normally distributed. As for the qualitative data, statistical differences and potential relations were assessed using Chi-Square test.

The degree of precision in the statistical tests conducted was estimated to be 95% i.e. the probability (P) of the assessed groups, to statistically differ from each other, when the P <0.05 this is statistically significant, when the P <0.01 this is statistically highly significant.

Correlation Coefficient:

Indicate the degree to which two measurs are related. It does not indicate why they are related or that one variable causes the other. It ranges from -1 to +1 when = 0 means no relationship.

RESULTS

A) Clinical Data:

1. **Gender**:
   Males and females were equally represented in both groups in the study. Group I included 10 patients, 6 of them were males (60%) and 4 of them were females (40%)while in group II, out of 10 patients, 6 were males (60%) and 4 were females (40%) (P value >0.05 NS).
2. **Age**:
   In group I the age of patients ranged from 29 to 46 with the mean age of 35.8±5.94 years while in group II it ranged from 18 to 49 with the mean age of 40.80± 6.052 years as shown in table (1) (P value >0.05 NS).
3. **Clinical presentation**:
   NIHSS was preformed to all patients included in the study. The NIHSS score can be classified into mild stroke 0-5, moderate stroke 6-10**,** moderately severe stroke 11-15**,** severe stroke 16-22& very severe stroke >22[8].

   Table (2) shows distribution scores of patients in both groups.

   Mean value of NIHSS in group I 5.6±3.1 while in group II 6.2±3.2. (p value >0.05 NS).

B) Radiological Findings:

1. **Size of the infarction**:
   In group I, evident small artery disease were reported in 2 patients (20%) while in group II none of the patients had small artery disease (0%) whereas in group I evidence of large artery disease was reported in 7 patients (70%) while in group II, all patients had large artery disease (100%), only 1 patient in group I had both small vessel disease and large vessel disease (P value >0.05 NS) so no significant statistical difference was reported between the 2 groups as regard size of the infarction.
2. **Site of the infarction**:
   In group I, 7 patients have ischemic infarction within the territory supplied by the anterior circulation (70%) while in group II all patients have ischemic infarction within the territory supplied by the anterior circulation (100%).

In group I, 3 patients have ischemic infarction within the territory supplied by the posterior circulation (30%) while none of the patiens of group II has infarction within the territory supplied by the posterior circulation (0%) (P value >0.05 NS).

C) Laboratory Findings:

1. Activated protein C resistance:

In group I none of patients has positive results regarding activated protein C resistance (0%) while in group II one patient was positive for activated protein C resistance (10%) as shown in table (3) and fig (1)(P value >0.05 NS) no significant statistical difference was reported between the 2 groups.

2. Homocystiene:

Homocystiene level was abnormally high in 2 patients in group I (20%) and normal in 8 patients (80%) with the mean value of 13.0±13.8 µmol/L.

In group II Homocystiene level was abnormally high in 2 patients (20%) and normal in 8 patients (80%) with the mean value of 7.94±3.6 µmol/L as shown in Fig. (2) and table (4) (P value >0.05 NS), so no significant statistical difference was reported between the 2 groups as regard serum homocysteine level.

3. MTHFR gene mutation:

None of the patients in both groups had the homozygous (TT) genotype the C677T MTHFR gene mutation.In group I, 7 patients had wild type of MTHFR gene (70%) while 3 patients have heterozygous C677T MTHFR gene mutation (30%).In group II, MTHFR gene was of wild type in 8 patients (80%) while 2 patients had heterozygous C677T MTHFR gene mutation (20%) as shown in Fig. (3) and table (5) (P value >0.05 NS). No significant statistical difference was reported between the 2 groups.

Fig. (4) shows C677T polymorphism in the MTHFR gene.

4. Relation of homocysteine level to C677T MTHFR gene mutation:

Homocysteine level less than 13 µmol/L is considered normal. A level between 13 and 60 µmol/L is considered moderately elevated, and a value greater than 60 to 100 µmol/L is severely elevated[13].

It was found that 2 patients in group I with mutant allele of MTHFR gene had moderately elevated (28.5 and 46.9 µmol/L).

While in the other patients in group I and II (whether having heterozygous MTHFR gene mutation or the wild type) serum homocysteine level was normal ranging between 4.9-12.2 µmol/L.

5. Thrombin antithrombin complex concentration (TAT):

In group I, 7 patients have abnormally high level of TAT (70%) while 3 patients have normal TAT level (30%) with the mean value of 8.9±7.6 ug/L.

In group II 8 patients have abnormally high level of TAT (80%) while 2 patients have normal TAT level (20%) with the mean value of 14.9±10.1 ug/L as shown in Fig. (5) and table (6).

However, this difference was statistically insignificant (P value >0.05 NS).

N.B. Normal TAT level 1.0 - 4.1 ug/L

D) Correlations of Laboratory and Clinical Findings:

Correlation between TAT, homocyteine level and NIHSS using correlation matrix study:

Correlation between TAT, homocyteine level and NIHSS using Correlation matrix study revealed presence of positive correlation between TAT level and NIHSS in group II (P value 0.025*, r value 0.699*) (Fig. 6). On the contrary such correlation was not found in group I (P value 0.740, r value 0.121) (Fig. 7).

Correlation between homocyteine level and NIHSS in both groups was non-significant.

Table 1. Age distribution in both groups.

Age (Ys)	**Group I (n= 10)**	**Group II (n= 10)**
Mean± SD	35.8± 5.94	40.80± 6.052

(P value >0.05 NS)

Table 2. NIHSS in both groups.

NIHSS	**Group I (n= 10)**	**Group II (n= 10)**
Mild 0-5	5 (50%)	5 (50%)
Moderate 6-10	4 (40%)	4 (40%)
Moderately severe 11-15	1 (10%)	1 (10%)
>16	0 (0%)	0 (0%)

(P value >0.05 NS)

Table 3. Activated protein C resistance in both groups.

Activated protein C resistance	**Group I (n= 10)**	**Group II (n= 10)**
Positive	0 (0%)	1(10%)
Negative	10(100%)	9(90%)

(P value >0.05 NS)

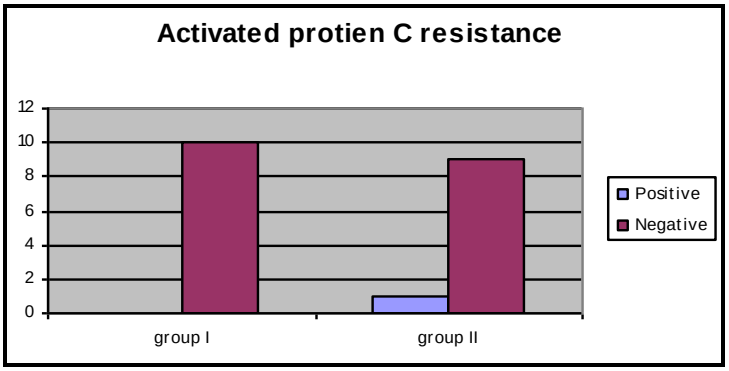


Fig. (1): Activated protein C resistance in both groups.

Table 4. Homocystiene level in both groups (P value >0.05 NS).

Homocystiene level (µmol/L)	**Group I (n= 10)**	**Group II (n= 10)**
Mean ±SD	13±13.8	7.94±3.6

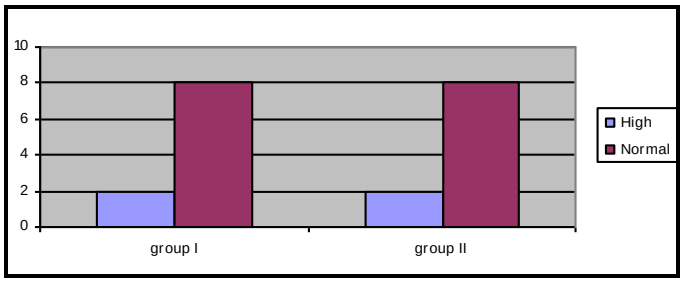


Fig. (2): Homocystiene level in both groups.

Table 5. C677T MTHFR gene mutation in both groups.

MTHFR gene	Group I (n=10)	Group II (n=10)
Heterozygous mutation	3 (30%)	2(20%)
Wild	7(70%)	8(80%)

(P value >0.05 NS)

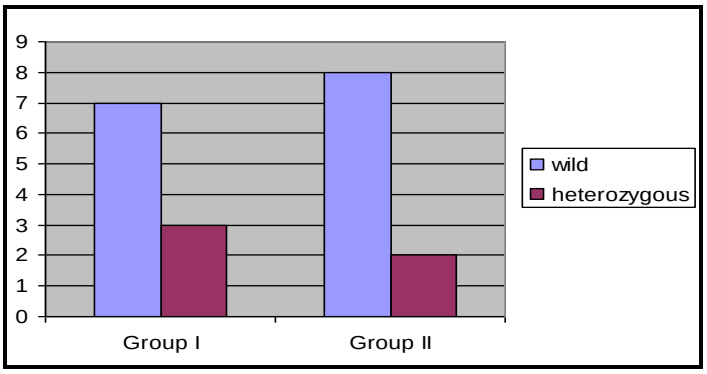


Fig. (3): C677T MTHFR gene mutation in both groups.

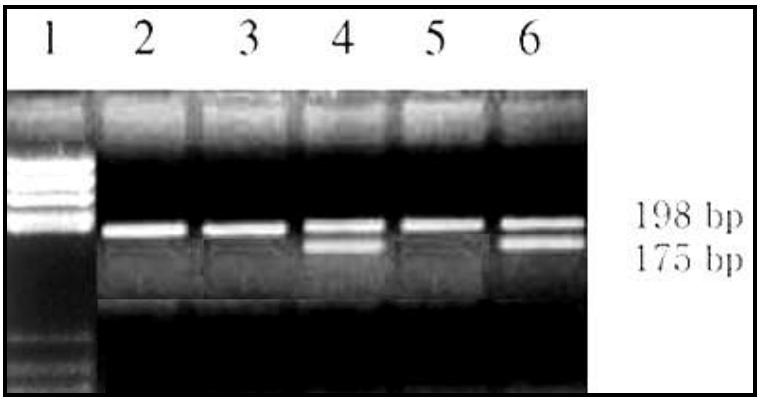


Fig. (4): C677T polymorphism in the MTHFR gene. Normal gene wild type lane 2, heterozygous mutant gene lane 3-6, marker lane 1.

Table 6. Thrombin antithrombin complex concentration (TAT) in both groups.

TAT level in ug /L	Group I (n=10)	Group II (n=10)
Mean ±SD	8.9±7.6	14.9±10.1

(P value >0.05 NS)

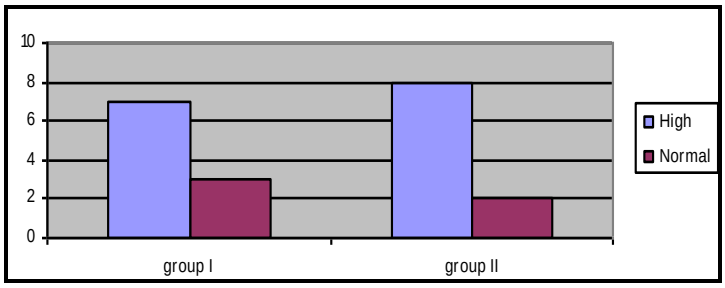


Fig. (5): Thrombin antithrombin complex concentration (TAT) in both groups**.**

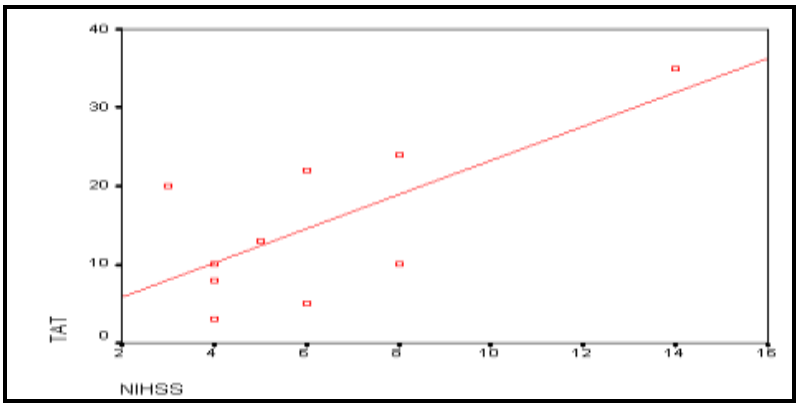
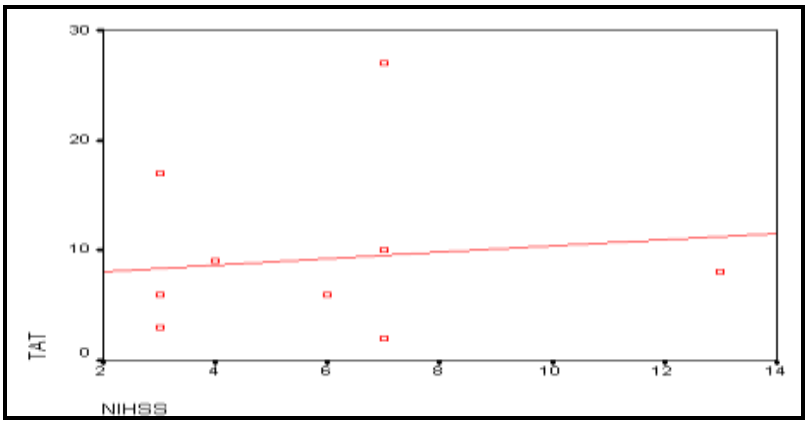


Fig. (6): Correlation between TAT and NIHSS in group I (P value >0.05 NS) .



(*) = (P value <0.05 S)

Fig. (7): Correlation between TAT and NIHSS in group II.

DISCUSSION

The aim of the current study was to unmask some of the hidden pathogenic mechanism underlying cryptogenic ischemic stroke through assessment of the role of some genetic polymorphism that induce thrombophilia after ruling out the presence of conventional vascular risk factors, these genetic disorders include; Activated protein C resistance (APC) and Common mutation (677C→T) in gene of Methylenetetrahydrofolate reductase (MTHFR) that lead to hyperhomocysteinaemia.

The current study aims also at investigating the role of thrombin-antithrombin complex concentration (TAT), as a marker of hypercoagulable state, in patients with cryptogenic ischemic stroke.

In the current study, all subjects are less than 50 years, this was because of the belief that the proportion of cryptogenic stroke among the young would be relatively high.

Activated protein C resistance:

No significant statistical difference was reported between the 2 groups (patients with cryptogenic stroke vs those with non-cryptogenic stroke) as regard activated protein C resistance (factor V Leiden).

This finding is consistent with the findings of many other studies that fail to find association between activated protein C resistance and cryptogenic stroke.

MTHFR (methylenetetrahydrofolate reductase enzyme) gene mutation and homocysteine level:

Previous reports have shown that hyperhomocysteinemia is closely associated with the occurrence of stroke, Perry et al[14] and Coull et al[15] identified hyperhomocysteinemia as a strong, graded, independent risk factor for stroke of any type.

As regard the relationship between the presence of C677T mutation in MTHFR gene and cryptogenic stroke, the current study showed no significant statistical difference between the 2 groups of patients (cryptogenic versus non-cryptogenic stroke) and none of patients in both groups had TT homozygous MTHFR gene mutation.

Regarding the relation between plasma homocysteine concentration & cryptogenic stroke, the current study found that although the mean value of homocystiene level in patients of group I (patients with cryptogenic stroke) was higher than mean value of homocystiene level in patients of group II but it did not reach statistical significance.

As regard the relationship between plasma homocysteine concentration, C677T mutation of methylenetetrahydrofolate reductase (MTHFR) gene the current study found that two patients in group I with the mutant allele T of MTHFR gene (heterozygous genotype) has moderately elevated serum homocystiene level while all other patients in group I and II (whether having the heterozygous genotype or the wild type) has normal homocysteine level.

The current study findings are consistent with that of other studies that failed to find association between heterozygous C677T mutation of methylenetetrahydrofolate reductase (MTHFR) gene and cryptogenic stroke. The current study findings are also consistent with that of the other studies regarding relationship between plasma homocysteine concentration, C677T methylenetetrahydrofolate reductase (MTHFR) gene mutation.

Pasquale et al.[16] and Endre et al.[17] reported that homozygosity for the TT mutation of the MTHFR gene in patients with ischaemic stroke was higher than controls but this difference was not statistically significant. They also found that total homocysteine levels were significantly higher in homozygotes for the MTHFR mutation (TT) than in heterozygotes (CT) and wild type homozygotes (CC), while total homocysteine levels in heterozygotes (CT) and wild type homozygotes (CC) show no significant difference.

However, Hiroyuki et al.[18] clearly demonstrated that the T allele of the MTHFR gene is associated with a high risk for common ischemic stroke.

Harland et al.[6]found that cryptogenic stroke was not associated with the MTHFR genotypes, and the T allele was associated only weakly and not statistically significant.

This is in contrast to a study by Markus et al.[19]who found that homozygosity for 677T MTHFR is a risk factor for arterial ischemic stroke (whether cryptogenic or non-cryptogenic).

In an Egyptian study by Shaheen et al.[20] the relation between hyperhomocysteinemia and mutant methylenetetrahydrofolate reductase gene was investigated in epileptic patients, it revealed that patients with heterozygous C677T mutation of methylenetetrahydrofolate reductase (MTHFR) gene had higher homocysteine level than those with normal gene and this difference was statistically significant.

These conflicting results of different studies including the current study regarding relation between the heterozygous MTHFR gene mutation and homocysteine level which can be explained by:

1. The concept of gene/environment interactions can clearly be applied for serum homocysteine level. The intake of folic acid, vitamins B_6 or vitamin B_{12} could ameliorate the effect of thermolabile MTHFR on homocysteine levels which could explain the normal homocysteine level in heterozygous (CT) MTHFR mutation[21].
2. The normal homocysteine level in heterozygous (CT) MTHFR mutation can also be explained by interaction with other genetic risk factors[22].

   None of our patients was homozygotes for the MTHFR mutation (TT) this can explain absence of hyperhomocysteinaemia.

Thrombin-Antithrombin complex concentration (TAT):

Antithrombin binds to thrombin to form an irreversible thrombin-antithrombin complex (TAT) that reflects generation of thrombin in vivo. Elevated TAT levels in IS might reflect the presence of ongoing thrombosis within cerebral vessels or may be a marker of systemic hypercoagulability[23].

Data concerning the relationship between ischaemic stroke and TAT levels are controversial[24]

In the current study, the mean value of TAT level was higher than normal in both groups.

However, the mean value of TAT level was higher in group II (patients with non-cryptogenic stroke) as compared to group I (patients with cryptogenic stroke) but this difference did not reach statistical significance difference.

These findings agreed also with van der Boom et al.[25] who reported that both elevated TAT levels have been observed in ischaemic stroke patients (whether cryptogenic or non-cryptogenic stroke).

Topcuoglu et al.[26] found also that in non-cryptogenic ischaemic stroke patients TAT levels have been reported to be increased.

In the current study, Positive correlation was found between TAT level and NIHSS in group II (patients with non-cryptogenic stroke).

This finding disagreed with Haapaniemi et al.[27], who did not find correlation between TAT levels and stroke severity or outcome.

Soncini et al.[28] found higher mortality in ischaemic stroke patients having increased TAT levels.

Bruno et al.[29] found no relationship between TAT levels and recurrence of ischaemic stroke.

The current study found no significant statistical difference as regard relation of TAT levels to the size of the infarction (small vessel disease vs large vessel disease).

This finding agreed with Haapaniemi et al.[27], who found that TAT levels showed no correlation with the size of the cerebral infarction.

However this finding disagreed with Takano et al.[30] who found that the larger the cerebral infarction the higher the TAT level.

These conflicting results of the above mentioned studies could be explained by:

1. TAT level is a reflection of hypercoagulable state not necessarily genetic in origin, acquired causes are also incriminated e.g. DM, use of drugs, this could explain that mean value of TAT level in group II (in whom such risk factors are present) was higher than group I.
2. The positive correlation between TAT level and size of the infarction found by some studies (on the contrary of the current study findings) could be related to secondary complications of the stroke rather than the infarction itself as mentioned by Haapaniemi et al.[27].

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الملخـص العربـــى

تقييم دور بعض القياسات الموقفة للنزف في مرضى السكتة الدماغية خفية السبب

في حوالي ثلث حالات مرضى الاحتشاء الدماغي لا يتم التوصل إلى سبب مباشر لحدوث مثل هذه الجلطات على الرغم من عمل كل الفحوصات المعملية اللازمة وهذا النوع من السكتة الدماغية يطلق عليه السكتة الدماغية خفية السبب.

تهدف هذه الدراسة إلى محاولة إماطة اللثام عن بعض الأسباب أو عوامل الخطورة التي قد تؤدي إلى حدوث السكتات الدماغية خفية السبب وخاصة الأسباب الوراثية الجينية منها .تشمل هذه الأسباب الوراثية الجينية والتي يتم فحصها في هؤلاء المرضى: مقاومة بروتين سي المنشط والطفرة الجينية الشائعة في الجين المنتج للأنزيم المختزل للميثيلين تتراهيدرو فوليت والتي قد تؤدي إلى ارتفاع نسبة الهوموسيستايين بالدم.تهدف هذه الدراسة أيضاً إلى دراسة دور تركيز مركب ثرومبين أنتي ثرومبين في البلازما والذي يعكس وجود قابلية أعلى لتخثر الدم لدي هؤلاء المرضى.

تم إجراء هذه الدراسة على 20 مريض من المرضى المصريين الذين يعانون من مرض السكتة الدماغية.تم تقسيم هؤلاء المرضى إلى مجموعتين تشتمل كل مجموعة على 10 مرضى: المجموعة الأولى تشتمل على المرضى الذين لم يتم فهيم التوصل إلى سبب واضح لحدوث الاحتشاء الدماغي (سكتة دماغية خفية السبب)، والمجموعة الثانية تشتمل على المرضى الذين تم التوصل فيهم إلى سبب واضح لحدوث الاحتشاء الدماغي (سكتة دماغية غير خفية السبب).وقد خضع هؤلاء المرضى لمجموعة من الفحوصات شملت أخذ التاريخ المرضي وعمل الفحص الإكلينيكي بالإضافة إلى مجموعة من الفحوصات المعملية والاشعات وقد توصلت الدراسة إلى النتائج الإحصائية الآتية:

- عدم وجود علاقة مباشرة بين كل من مقاومة بروتين سي المنشط، الطفرة الجينية للجين المنتج للأنزيم المختزل للميثيلين تتراهيدرو فوليت، تركيز مركب ثرومبين – أنتي ثرومبين فى البلازما والسكتة الدماغية خفية السبب.
- وجود علاقة مباشرة بين تركيز مركب ثرومبين – أنتي ثرومبين في البلازما والحالة الإكلينيكية لمريض السكتة الدماغية غير خفية السبب.
- عدم وجود مؤشر لارتفاع نسبة الهوموسيستايين بالدم في المرضى الذين يعانون (الطفرة الجينية الغير متجانسة) بالمقارنة بالمرضى الذين لا يعانون من هذه الطفرة الجينية.

وقد قدمت الدراسة المقترحات الآتية:

- تقترح الدراسة امتداد الأبحاث لعدد أكبر من المرضى وذلك للمزيد من توثيق النتائج.
- عدم إجراء تحليل مقاومة بروتين سي المنشط أو تركيز مركب ثرومبين – أنتي ثرومبين في البلازما لمرضى السكتة الدماغية خفية السبب و عدم إجراء تحليل الطفرة الجينية للجين المنتج للأنزيم المختزل للميثيلين تتراهيدرو فوليت إلا للمرضى الذين يعانون من ارتفاع نسبة الهوموسيستايين.
- يمكن استخدام تركيز مركب ثرومبين–أنتي ثرومبين بالبلازما كدلالة على مدى خطورة الجلطة الدماغية غير خفية السبب وكدلالة على التأثير طويل المدى لها.