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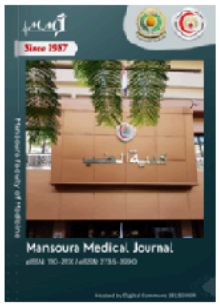

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ACTIVATED PROTEIN C RESISTANCE IN MIDDLE AGE PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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ACTIVATED PROTEIN C RESISTANCE IN MIDDLE AGE PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Homeostatic imbalance may be an etiological factor in the development of acute coronary syndrome. Inherited resistance to activated protein C (APC) is a common disorder associated with hypercoagulability and lifelong risk of venous thrombosis. APC resistance is due to a single mutation in the gene coding for coagulation factor V (FV:Q506). The association of APC resistance with arterial thromboembolic disease, however, is still controversial. This study aimed to investigate the role of APC resistance in coronary artery thrombosis. We have studied the APC resistance (assessed by the ratio of the aPTT with and without added APC) in 66 adult patients under 50 years of age presenting with acute myocardial infarction. In addition, plasma levels of anti-thrombin III (by coagulation method assay), protein S (by radial immunodiffusion) and protein C activity (by coagulation method) were also determined. The results were compared with those of 16 apparently healthy individuals with matched age and sex without any thromboembolic events or bleeding tendency in their past history. APC resistance phenotype was considered positive when the APC sensitivity ratio was below or equal to the cut-off value of 2.1. It was detected in one control subject (6.25%) and in 12 patients with acute myocardial infarction (18.2%). The APC ratio was negatively correlated with LDH and AST (p values: <0.05 and <0.01 respectively) but not correlated with the lipid parameters or CK (total & MB). A stepwise multiple regression analysis revealed that LDH was the only

thrombin III) as well as contribution of some thrombogenic risk factors in AMI aiming to study their prevalence in AMI patients.

SUBJECTS

This study was conducted on 66 patients (54 males and 12 females) presenting with acute myocardial infarction. Their ages ranged from 25 to 49 years. They were selected from those admitted to coronary care unit, Mansoura University Hospital. In addition, 16 apparently healthy individuals with matched age and sex were selected by thorough clinical examination and laboratory investigations to serve as a control group.

**Inclusion Criteria :* The patients included in the study were selected so that at least 2 months have passed from the last thromboembolic episode in order not to affect the results of coagulation assays. The diagnosis of acute MI was based on elevated cardiac enzymes; creatine phosphokinase (CK), CK-MB more than twice the upper limit of the referance range and lactic dehyrogenase (LDH) and ECG changes that include S-T segment elevation of at least 2 mm,0.08 seconds from the J point in at least two related electrical fields,with typical evolutionary changes ,appearance of a new Q waves in at least two related leads NB : Samples were taken within 6 hours after the onset of pain and prior to administration of anticoagulant drugs.

**Exclusion criteria :* All patients who had a disease that is known to affect the results of the homeostatic studies such as chronic liver disease, renal diseases especially nephrotic syndrome and DIC were excluded. Also, pregnant females or those using oral contraceptive pills were excluded from the study.

METHODS

The cases of the study were subjected to:

1- Clinical assessment :

Accurate history taking with special stress on family history, past history of similar condition and on the risk factors for arterial thrombosis such as hypertension, diabetes mellitus, cigarette smoking and lipid disorders.

Thorough physical examination.with stress on the heart and vascular assesment

2- Laboratory investigations :

** Routine Investigations :*

RESULTS

Table (1) represents the statistical analysis of prothrombin time (PT), activated partial thromboplastin time (aPTT), antithrombin III (AT III) concentration, protein C (PC) activity and protein S (PS) antigen level in different studied groups. AT III was significantly decreased in cases with acute myocardial infarction (AMI) and positive APC resistance phenotype when compared to those with negative APC resistance phenotype and to the control group ($p<0.05$). On the other hand, protein C activity did not differ among various groups ($p>0.05$).

The APC resistance phenotype was detected in 6.25% and 18.2% of control and patient groups respectively as shown in table (2).

The correlation statistics between the APC-SR and other studied coagulation parameters revealed that it was significantly positively correlated with aPTT, AT III concentration, protein S level and protein C activity ($p<0.05$) but not with PT ($p>0.05$) {Table 3}.

On the other side, the APC-SR was negatively correlated with LDH and AST (p values: <0.05 and <0.01 respectively) with non significant correlation with lipogram parameters, CK (total) and CK(MB) {$p>0.05$, Table 4}.

To study the most predictor factor of APC sensitivity ratio, predictors found to be significant at unvariate analysis {ATIII, protein C, protein S and biochemical tests including cholesterol, triglycerides, LDL, CPK (total and MB), AST and LDH} were entered into multiple regression model using stepwise technique (Table 5). The results revealed that only LDH was significantly correlated with APC-SR.

Among the studied thrombogenic risk factors, hypertension was found to be the most important factor in patients with AMI with or without APC R phenotype (Table 6).

Table (4): Correlation between APC resistance ratio and cholesterol, triglycerides, HDL, LDL, CPK (total), CPK (MB), LDH and AST.

	APC-SR	
	r	*p*
Cholesterol (mg/dl)	0.190	> 0.05
Triglycerides (mg/dl)	0.160	> 0.05
HDL (mg/dl)	0.039	> 0.05
LDL (mg/dl)	0.105	> 0.05
CPK-total (U/L)	0.042	> 0.05
CPK-MB (U/L)	0.113	> 0.05
LDH (U/L)	0.272	< 0.05
AST (U/ml)	0.583**	< 0.001

Table (5): Stepwise multiple regression for prediction of APC ratio.

Model	β	SE of β	t-test	p-value
Constant	2.98	0.1	29.84	0.000
LDH	0.0037	0.000	2.32	0.23

R= 0.25, R^2= 0.063, Model F (ANOVA)= 5.37, p= 0.023

Table (6): Thrombogenic risk factors in AMI patients with and without APC resistance phenotype.

		APC< 2.1 (n =12) No (%)	APC> 2.1 (n =54) No(%)	Sign Test
Diabetes Mellitus	Yes	8 (66.7)	22 (40.7)	X2 2.6
	No	4 (33.3)	32 (59.3)	NS
Hypertension	Yes	8 (66.7)	42 (77.8)	Fisher exact
	No	4 (33.3)	12 (22.2)	P <0.01
Smoking	Yes	-	22(40.7)	Fisher exact
	No	12(100)	32(59.3)	P<0.01

agreement with those reported by Yetkin et al(17) who reported that APC-R is an independent risk factor for myocardial infarction.

In the comparative study among the categories of AMI, data revealed significant decreases of AT III concentration and protein S antigen level in AMI patients with positive APC resistance phenotype when compared to those with negative APC resistance phenotype ($P<0.05$). In addition, a significant positive correlation was encountered between APC resistance ratio and APTT, ATIII, protein C and protein S ($P<0.05$) So we can suggest that low levels of these anticoagulant proteins may be associated with low functional activated protein C activity.

Among patients with AMI, 40.7% were current smokers and all did not exhibit the APC resistance phenotype. On the other hand, 66.7% of patients with positive APC resistance phenotype were diabetic and also 66.7% were hypertensive. However, no significant correlation was found between APC-R ratio and biochemical parameters (cholesterol, triglycerides, HDL, CPK-total and CPK-MB). In contrast, a significant positive correlation was elicited with both LDH ($P<0.05$) and AST ($p<0.001$).

Further analyses were undertaken to identify the possible interaction between APC resistance phenotype and biochemical parameters (cholesterol, triglycerides, LDL, CPK-total, CPK-MB, LDH, AST). To overcome the differences between the patients and controls, these variables as well as protein C, protein S and AT III were included in a multivariate stepwise logistic regression model. It revealed that only LDH was significantly correlated with APCR phenotype. Consistent with our data is the finding of synergistic effect that was recently reported in a cohort of older patients with myocardial infarction. (18,19) The multiple correlations found among these variable may underscore their complex interactions in acute coronary events.

Our data suggested a synergistic effect of thrombogenic risk factors in the pathogenesis of AMI. Furthermore, APC resistance phenotype and clinical cardiovascular risk factors may result in an additive risk for acute myocardial infarction.

From this study, we can conclude that, unlike conventional risk factors,

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مقاومة بروتين "سى" النشط فى مرضى الاحتشاء البطينى الحاد للقلب ذوى الأعمار المتوسطة

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يعتبر الخلل فى عملية التجلط من الأسباب المباشرة فى حدوث الاحتشاء البطينى الحاد للقلب، وقد لوحظ أن مقاومة بروتين سى النشط الوراثى الذى ينتج من حدوث طفرة فى الجين المسئول عن معامل التجلط رقم (٥) من الأمراض الشائعة التى لها علاقة بزيادة تجلط الدم خاصة الجلطات الوريدية. وقد اختلفت الآراء حول دورة فى حدوث الجلطات الشريانية.

ولتوضيح دور مقاومة بروتين "سى" النشط فى حدوث تجلط الدم الشريانى، أجريت هذه الدراسة على ٦٦ مريض بالاحتشاء البطينى الحاد للقلب بوحدة العناية المركزة للقلب بمستشفى المنصورة الجامعى وقد تراوحت أعمارهم بين ٢٥ الى ٤٩ عام بالاضافة الى ١٦ من الأصحاء كمجموعة ضابطة .

وتم تعين نسبة مقاومة بروتين "سى" النشط وبروتين "سى" وبروتين "اس" ومضاد الثرومبين - ٣ فى بلازما المرضى والأصحاء وذلك بالاضافة الى صورة الدهون وانزيم (CK الكلى وCK- MB) فى السيرم. واعتبر المريض مقاوماً لبروتين "سى" النشط اذا كانت النسبة أقل من أو تساوى ٢٠١ وقد كانت إجابية فى ٢٥ر٦٪ من المجموعة الضابطة و ٢ر١٨٪ من المرضى. أما بالنسبة لبروتين "سى" وبروتين "اس" ومضاد الثرومبين -٣ فلم يوجد أى إختلاف ذو دلالة احصائية مع المجموعة الضابطة .

وأظهرت نتائج البحث أيضاً وجود علاقة إيجابية ذو دلالة إحصائية بين مقاومة بروتين "سى" النشط وكل من انزيم اللاكتيك ديهدروجنيز (LDH) وانزيم (AST) بينما لاتوجد علاقة ذو دلالة احصائية مع مستوى الدهون وانزيم(CK الكلى وCK - MB) فى مصل المرضى. كما أثبتت النتائج أن انزيم (LDH يعتبر من العوامل الهامة للتنبؤ بوجود مقاومة بروتين "سى" النشط فى مرضى الاحتشاء البطينى الحاد للقلب.

ونستخلص من الدراسة الحالية أن مقاومة بروتين "سى" النشط يعتبر من الأخطار الوراثية التى قد تسبب الإصابة المبكرة بالاحتشاء البطينى الحاد للقلب .