Inflammatory Markers and Stroke: The Relationship

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معلمات الالتهابات والسكتة الدماغية: العلاقة

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الخلاصة:
الهدف: تقييم العلاقة بين معلمات الألتهاب ، البروتين التفاعلي- سي وخلايا الدم البيضاء والسكتة الدماغية
تصميم الدراسة: دراسة سريرية إستباقية
مكان إجراء الدراسة: مستشفى الصدر التعليمي في البصرة/ العراق
طرق العمل: في هذه الدراسة تم شمول ٧٣ مريضاً بالسكتة الدماغية (٤٢ ذكرا" و ٣١ أنثى) ،و٧٥ من الاصحاء (٤٥ ذكرا"و ٣٠ أنثى) كمجموعة ضابطة. تم قياس كل من، البروتين التفاعلي-سي ، خلايا الدم البيضاء ، سكر الدم، الكولسترول الكلي، الدهون الثلاثية، البروتينات الدهنية عالية الكثافة والبروتينات الدهنية واطئة الكثافة لدى كل من المرضى و الأصحاء.
النتائج: ظهر ان مستويات كل من البروتين التفاعلي-سي و خلايا الدم البيضاء كانت مرتفعة بشكل معنوي لدى مرضى السكتة الدماغية من الذكور بالمقارنة مع الأصحاء (ب< ٠.٠٠١). وكانت تراكيز كل من سكر الدم، الكولسترول الكلي، الدهون الثلاثية، البروتينات الدهنية واطئة الكثافة كانت مرتفعة بشكل معنوي، بينما كانت البروتينات الدهنية عالية الكثافة منخفضة بشكل معنوي لدى المرضى بالمقارنة مع الأصحاء (ب< ٠.٠٠١). أما لدى الإناث فقد كانت مستويات كل من البروتين التفاعلي- سي (ب< ٠.٠٥). و خلايا الدم البيضاء (ب< ٠.٠٠١) كانت مرتفعة بشكل معنوي لدى مرضى السكتة الدماغية مقارنة مع الأصحاء. وكانت تراكيز كل من سكر الدم، الكولسترول الكلي، الدهون الثلاثية، البروتينات الدهنية واطئة الكثافة كانت مرتفعة بشكل معنوي، بينما كانت البروتينات الدهنية عالية الكثافة منخفضة بشكل معنوي لدى المرضى بالمقارنة مع الأصحاء (ب< ٠.٠٠١).
الاستنتاجات: توجد علاقة معنوية بين معلمات الألتهاب ، البروتين التفاعلي-سي وخلايا الدم البيضاء والسكتة الدماغية. هذه العلاقة قد تسند الدور المفترض للالتهابات والأخماج في نشوء و تطور تصلب الشرايين ومضاعفاته.

Abstract
Objective: To evaluate the relationship between markers of inflammation markers, C-reactive protein (CRP) and leukocytes, and stroke.
Design: A prospective clinical study.
Setting: Al-Sadr Teaching Hospital, Basrah, Iraq
Patients and Methods: In this prospective study,73 patients (42 males and 31 females) with acute stroke and 75 control subjects (45 males and 30 females) were included. CRP concentration, leukocyte count, fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high density lipoprotein- cholesterol (HDL-C), and low density lipoprotein-cholesterol (LDL-C) level were determined in patients and controls.
Results: CRP and leukocytes were significantly higher among male patients with acute stroke compared to controls ($p<0.001$). FBG, TC, TG and LDL-C concentrations were significantly higher whereas HDL-C level was significantly lower among patients compared to controls ($p<0.001$). In females, CRP ($P<0.05$) and leukocytes ($P<0.001$) were also significantly higher among patients in comparison to controls. FBG, TC, TG and LDL-C concentrations were significantly higher while HDL-C level was significantly lower among patients compared to controls ($p<0.001$).

Conclusion: A significant relationship exists between CRP and leukocytes, and stroke. This relationship could support the plausible role of inflammation and infection in the development and progression of atherosclerotic disease and its complications.

Introduction

Stroke is the most common clinical manifestation of cerebrovascular disease which represent one of the clinical end points of atherosclerosis. It ranks among the leading causes of death and disability world-wide.[1-4]

The pathophysiology of atherosclerosis and cardiovascular disease (CVD) have been extensively revolutionized with the introduction of new cardiovascular (CV) risk factors beside the classical ones. Among the new risk factors, are infections particularly with Chlamydia pneumoniae (C. Pneumoniae),[5,6] Helicobacter pylori[7,8] and viruses,[9,10] and a wide variety of haemostatic variables including elevated plasma levels of homocystein,[11-13] C-reactive protein (CRP),[14-16] fibrinogen[17-19] and other factors.[17,18,20,21]

The evidence supporting the role of inflammation and inflammatory markers in the pathophysiology of atherosclerosis and its clinical sequel is now well established.[22,23] Atherogenesis is essentially an inflammatory response to a variety of risk factors, and consequently this response may in turn result in the development of acute coronary and cerebrovascular syndromes.[24]

A diversity of inflammatory markers have been investigated in association with cerebrovascular disease including fibrinogen,[25,26] homocystein,[12,27], CRP, [28,29] leukocytes,[30,31] cytokines,[31,32] D-dimer,[33] plasminogen activator inhibitor-1 activity,[33] and factor VIIC[33] and other suggested factors.[31,34,35] The identification of the inflammatory background of the atherosclerotic process may provide potential advantage in the introduction of inflammatory markers as indicators for atherogenesis and predictors for its clinical consequences.[24] Furthermore, it has been suggested that inflammatory and haemostatic markers may have a predictive value in ischaemic stroke,[33] and also, the characterization of these markers and the identification of their therapeutic targets may carry the potential advantage in employing effective therapeutic interventions for cerebrovascular disease.[36]

This study is an attempt to evaluate the association between the inflammatory markers, CRP and leukocytes, and stroke.

Patients and Methods

In this a prospective study, conducted from September, 1st, 2005 throughout December 2007, 73 patients with acute stroke were included. They were 42 males and 31 females, 35-80 years of age. They were admitted to the medical ward in Al-Sadr Teaching Hospital, Basrah, Iraq. The diagnosis of acute stroke was based on both, the clinical findings and the results of imaging tests, brain computed tomography (CT) scan and/or magnetic resonance imaging (MRI). In addition, 75 apparently healthy subjects, 45 males and 30 females, 36-72 years of age, with no history of CVD, type 2 diabetes (T2D) or hypertension were included as a control group.

Blood specimen were collected in a fasting state and divided into 2 parts. The first was anticoagulated with sodium citrate and used for the estimation of leukocyte count.[37] Whereas serum was separated from the second part and used for the estimation of CRP, fasting blood glucose (FBG) and lipid profile. CRP concentration was determined using diagnostic kit from BioMaghreb, Tunis. FBG, total cholesterol (TC), triglycerides (TG)

and high density lipoprotein- cholesterol (HDL-C) levels were estimated by enzymatic methods using kits from bioMerieux, France . Low density lipoprotein- cholesterol (LDL-C) level was calculated using the following equation.[38]

LDL-C = TC-(HDL-C + TC /5).

Statistical analysis was performed using Chi-square(X^2) and t-tests. $P<0.05$ was considered statistically significant.

Results

The characteristics of patients with acute stroke and controls are presented in Table 1. Body mass index (BMI) = Kg/m^2 ($P<0.01$), Systolic blood pressure (SBP), ($p<0.001$) and diastolic (DBP) blood pressure ($p<0.001$) were significantly higher among male as well as female stroke patients compared to controls. Although the frequency of cigarette smoking was higher among patients with acute stroke in either sex in comparison to normal subjects, however, the differences were statistically not significant ($P>0.05$).

As shown in Table 2. CRP and leukocytes were significantly higher among male patients with acute stroke compared to controls ($p<0.001$). In addition FBG, TC, TG and LDL-C concentrations were significantly higher while HDL-C level was significantly lower among patients compared to control subjects ($p<0.001$).

The results in females are presented in Table 3. Similarly, female patients showed significantly higher CRP and leukocytes compared to female controls ($P<0.05$ and $P<0.001$ respectively). Also, FBG, TC, TG and LDL-C concentrations were significantly higher whereas HDL-C level was significantly lower among patients compared to controls ($p<0.001$).

Table 1. Characteristics of stroke patients and control subjects.

Characteristic	Male patients (n=42)	Male controls (n=45)	Female Patients (n=31)	Female controls (n=30)
Age (years)	56.4 (11.8)	53.1 (10.2)	54.9 (9.7)	51.4(11.1)
BMI (Kg/m^2)	26.4 (5.1)**	23.9 (3.0)	27.9 (5.5)**	24.4(3.0)
SBP (mm.Hg)	161.3 (24.8)***	124.9 (11.3)	157.6 (25.5)***	121.8(12.8)
DBP (mm.Hg)	100.5(10.9)***	83.3 (7.8)	98.4 (10.6)***	79.7(9.7)
Cigarette smoking: n(%)	23 (54.8%)$^{+}$	16 (35.6%)	3(9.7%)$^{++}$	2(6.7%)

Values are expressed as mean (SD).

** : $P<0.01$ (Male patients vs male controls, female patients vs female controls)

***: $P<0.001$(Male patients vs male controls, female patients vs female controls)

\+ : $X^2 = 3.282$, $P>0.05$, D.F = 1 (Male patient vs male controls)

++ : $X^2 = 0.184$, $P>0.05$, D.F = 1 (Female patients vs female controls)

Table 2. CRP level, leukocyte count and biochemical parameters among male stroke patients and male controls

Parameter	Patients (n=42)	Controls (n=45)
CRP (mg/l)	16.6 (13.8)***	7.7(4.2)
Leukocytes (10^9/L)	10.5(2.6)***	7.4(1.9)
FBG (mg/dl)	152.5 (47.8)***	93.9(10.1)
TC (mg/dl)	209.2 (25.4)***	183.7(15.4)
LDL-C (mg/dl)	133.8 (24.8) ***	109.0(15.0)
TG (mg/dl)	187.8 (43.2)***	142.3(33.2)
HDL-C (mg/dl)	37.8 (6.3)***	46.5(6.7)

Values are expressed as Mean (SD)
*** : $p < 0.001$

Table 3. CRP level, leukocyte count and biochemical parameters among female stroke patients and female controls

Parameter	Patients (n=31)	Controls (n=30)
CRP (mg/l)	13.5 (11.5)*	8.4 (4.9)
Leukocytes(10^9/L)	10.1(2.3)***	7.4(2.0)
FBG (mg/dl)	160.4 (41.7)***	91.6 (7.6)
TC (mg/dl)	211.7 (32.8)***	184.8(14.8)
LDL-C (mg/dl)	136.2 (36.3) ***	107.0(16.4)
TG (mg/dl)	182.6 (51.5)***	137.1 (30.1)
HDL-C (mg/dl)	39.0 (5.9)***	52.4(6.0)

Values are expressed as Mean (SD).
*: $p<0.05$
*** : $p < 0.001$

Discussion

Atherosclerosis is clearly an inflammatory process.[21,39-41] It does not simply due to lipid accumulation.[41] Also, an immune background to atherosclerotic disease had been proposed.[42] All stages of the development of atherosclerotic disease may represent an inflammatory response to injury.[24] Inflammation, thrombosis and atherosclerosis are interdependent and may represent a triad within the complex pathogenic process of atherothrombosis.[22] Cytokines and other bioactive molecules, a key factor in inflammation, are believed to be involved in every step of atherogenesis. Cytokines may be involved in vascular inflammation and promotes the production of endothelial adhesion molecules, proteases and other inflammatory mediators, and also, may induce the formation of interleukin–6 which stimulate the liver to increase the production of acute phase reactants like CRP.[24,43] Furthermore, it has been suggested that a link

exists between inflammation and coagulation cascade during the evolution of atherothrombotic disease.[44]

An infective background to atherosclerotic disease has also been suggested. Atherosclerosis is a chronic inflammatory process, and a variety of common chronic infections have been proposed to contribute to the inflammation of the vascular wall that results in atherosclerosis.[45,46] Chronic bronchitis is among those chronic infections that increase the risk of stroke.[47,48] A high frequency of flu-like illnesses may also be a stroke risk factor.[47] A recent infection has been also observed as a significant and independent risk factor for stroke[43]. Furthermore, investigators have recently found preliminary evidence that the aggregate burden of these chronic infections, rather than any single organism, may contribute to atherosclerosis and the risk of clinical vascular events, including ischemic stroke.[45] Moreover, it has been found that *C. pneumoniae* infection may promote atherogenesis by either modifying CRP, fibrinogen, lipid and lipoprotein levels or by affecting macrophage function.[49] Stroke patients showed an elevated antibody titer to *C. pneumonia*.[50] However, the increased levels of markers of inflammation may represent signs of an active chronic infection.[51]

The present study demonstrated a significant elevation in CRP concentrations as well as leukocyte count among patients with acute stroke in comparison to normal subjects, a result which is consistent with the observation of others.[30,52,53] This finding focused a light on strength of the association between markers of inflammation and stroke. Inflammation can potentiate the coagulation pathways via different mechanisms, and may inhibit anticoagulant mechanisms.[43] These disorders may play a crucial role in the development of infection-associated stroke. It has been suggested that inflammatory markers, beside they are risk factors for atherosclerotic disease, however, they might represent a response to other conventional CV risk factors, or due to inflammatory response as a part of the atherosclerotic process.[24] Ischaemic stroke is associated with a transient rise in fibrinogen, leukocytes and cytokines that occurs as an acute phase response.[43] Inflammatory interactions that occur at the blood-endothelium interface, involving cytokines, adhesion molecules, chemokines and leukocytes, are vital to the pathogenesis of tissue damage in cerebral infarction.[31] The interacting leukocytes which appear in the vascular intima and lumen may be used as predictive biomarker for atherosclerosis and restenosis after treating CVD.[54] Leukocytes could serve as an independent risk factor for all-cause mortality and for atherosclerotic mortality.[55]

This study also clearly demonstrated that patients with acute stroke tend toaccumulate multiple adverse CV risk factors including over weight, high SBP and DBP, an elevated FBG and an abnormal lipid and lipoprotein profile. Inflammatory markers may have a joint effect with conventional CV risk factors resulting in an additive CVD risk.[56] CRP also has the capacity to interact with other risk factors to increase the risk for T2D and CVD.[57] In addition, an elevated levels of inflammatory markers were positively associated with insulin resistance (IR).[58] Furthermore, a combination of IR and inflammation resulted in a higher degree of coronary artery disease in both Caucasians and African Americans. These observations suggest that inflammation may potentiate the CV risk factor role of IR.[59]

A diversity of Inflammatory markers were independently associated with CVD and atherothrombotic events,[15,16,24,26,33,55,60-62] with CRP considered as the best characterized marker for CVD risk, and also, an independent predictor of future CV events as well as stroke risk and prognosis.[15,28,29,57,63,64] There is a substantial clinical evidence suggesting that many inflammatory biomarkers of are increased years in advance of first

ever acute coronary event or thrombotic stroke, and that these biomarkers are highly predictive of recurrent myocardial infarction or stroke, T2D, and CV death[29]. However, it has been proposed that CRP may not be a good predictor of the extent of atherosclerotic disease.[24] Also, the evidence supporting the use of CRP as a screening test in primary prevention of stroke and CVD may be inadequate yet.[24,65]

We conclude that a relationship exists between markers of inflammation, CRP and leukocytes and cerebrovascular disease. Such significant association may focused a light on the inflammatory basis of stroke, and also, on the debatable role of infections in the pathophysiology of atherosclerosis and cerebrovascular disease. The confirmation of the potential and plausible role of inflammation in in the pathogenesis of atherosclerotic disease may pave the way to the inclusion of
anti-inflammatory drugs in the therapeutic modalities for the clinical consequences of atherosclerotic disease including stroke.

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