Research Article

The Role Of Acute Phase Reactants In Acute Ischemic Stroke

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Abstract

Inflammatory factors play an important role in the pathogenesis of ischemic stroke. The aim of our study was to determine the influence of fibrinogen, C-reactive protein and other acute-phase reactant levels in acute ischemic stroke. This study involves forty -three patients. The control group was formed out of thirty-seven. The blood samples were drawn to measure serum fibrinogen, ferritin, CRP levels, white blood cell (WBC), erythrocyte sedimentation rate (ESR). Within 24-72 hours, the patients serum fibrinogen, ferritin and CRP values were higher than the control group. In addition, the levels of fibrinogen and CRP were found to be higher than the patients whose clinical health was poor. Acute phase proteins level such a fibrinogen, CRP, ferritin increase after acute ischemic stroke. These findings support a possible role of an inflammatory stimulus in the acute ischemic stroke.

Keywords: Acute Ischemic Stroke, Fibrinogen, Acute Phase Reactants

INTRODUCTION

Stroke is the third cause of mortality and the first cause of disability. Recent literatures have demonstrated that inflammation contributes to all phases of atherosclerosis. The results of researches suggest that atherosclerosis is an inflammatory disease. In acute phase of cerebrovascular diseases, biochemical markers of inflammation could be useful to predict severity of stroke. Fibrinogen is a well known acute phase protein and risk factor for myocardial infarction and stroke. High fibrinogen levels represent an acute phase response in early acute stroke. One of other inflammatory markers, such as CRP strongly predicts the risk of carotid stenosis, first stroke and post stroke mortality. In addition, increased CRP levels are related with poor prognosis in short follow-up period. There are some evidences about the significant role of iron in cerebral damage. The role of iron in acute ischemic stroke has been investigated; as a result of this research, there may be relationship between high iron level and poor prognosis.

In this study, we aimed to evaluate the role of fibrinogen, C-reactive protein and other acute-phase proteins levels in the patients with acute ischemic stroke, in acute period (the first 24-72 hours).
METHODS

Forty-three patients (23 female, 20 male) who have been diagnosed as acute ischemic stroke, in neurology department of Ankara Hospital, between June 2001 and December 2001 were included in this study. The average of ages was 64.9±11.6.

The control group, age and sex matched, included 37 people (24 female, 13 male), admitted to neurology clinic, all of them have no known vascular risk factors. In control group, the average of ages was 62.4±12.

Exclusion criteria for all subjects were trauma, severe liver disease, renal failure, cancer, cerebral hemorrhage, acute myocardial infarct, deep vein thrombosis, anti-coagulant or iron treatments, chronic inflammatory diseases, fever or acute inflammatory or infectious conditions. In addition, there weren’t any surgical operation or invasive operations (e.g. angiography) within the last 3-6 months.

CT scan of the brain was performed in first 24-72 hours for all patients. Blood samples were obtained within 24-72 hours after qualifying stroke. Serum fibrinogen, ferritin, CRP, white blood cell (WBC) and erythrocyte sedimentation rate (ESR) were measured.

The fibrinogen level was measured by Date Behring automation; the normal range is 189-350 mg/dl. The levels of CRP were determined by immuno nephelometric, latex-enhanced assay (Dade Behring).

The time of stroke was indicated as the period between the initiation of stroke and the time the blood sample had been obtained.

The stroke severity score (SSS) performed by Wang was used to determine the degree of affection from stroke (26) (Table I). In this scale the high score indicates severity of the stroke.

Table I: Stroke severity classification

<table>
<thead>
<tr>
<th>Consciousness level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consciousness (0)</td>
</tr>
<tr>
<td>Subconsciousness (1)</td>
</tr>
<tr>
<td>Unconsciousness (2)</td>
</tr>
</tbody>
</table>

Aphasia

<table>
<thead>
<tr>
<th>Mixed aphasia (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensorial aphasia (1)</td>
</tr>
<tr>
<td>Motor aphasia (1)</td>
</tr>
<tr>
<td>Absent of aphasia (0)</td>
</tr>
</tbody>
</table>

Cranial nerve involvement (CNI)

<table>
<thead>
<tr>
<th>Tree CNI (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two CNI (2)</td>
</tr>
<tr>
<td>One CNI (1)</td>
</tr>
<tr>
<td>No CNI (0)</td>
</tr>
</tbody>
</table>

Motor examination

<table>
<thead>
<tr>
<th>Quadriplegia (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemiplegia (3)</td>
</tr>
<tr>
<td>Hemiparesis (2)</td>
</tr>
<tr>
<td>Monoparesis (1)</td>
</tr>
<tr>
<td>None (0)</td>
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</tbody>
</table>

Sensory examination

<table>
<thead>
<tr>
<th>Hypoestesia (+) (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoestesia (-) (0)</td>
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Cerebellar examination

<table>
<thead>
<tr>
<th>Bilateral involvement (2)</th>
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<tbody>
<tr>
<td>Unilateral involvement (1)</td>
</tr>
<tr>
<td>None (0)</td>
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</table>

Urinary incontinence

<table>
<thead>
<tr>
<th>Positive (1)</th>
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<tbody>
<tr>
<td>Negative (0)</td>
</tr>
</tbody>
</table>
RESULTS

There was no difference between the age of patient and control group (\(p>0.005\), \(t\) test).

The fibrinogen level was higher in patient group (\(p<0.001\)).

The ferritin (102.6±7) and CRP (25.5±3) (mean=10.5) values of patient group were higher than the control group (63±5) (median=51.3) (\(p<0.01\)), (4.8±3) (mean=3.13) (\(p<0.001\)) within 3 days. WBC counts in the patients (10 062 ±37) were higher than the control group (7 200±16) (\(p<0.001\)).

Regarding the levels of hematocrit (\(p>0.05\)), iron (\(p>0.01\)), transferrin (\(p>0.05\)), capacity of binding total serum iron (\(p>0.05\)), ESR values (29.8±16) (mean=24) (23.8±13) (mean=21) and platelet counts (250 697,8±74) (265 783,8±55) (\(p>0.05\)); there were no difference between two groups.

By using spearman correlation analysis, there was a relationship between fibrinogen levels of patients and stroke severity score (\(p<0.05\))(\(r=3814\)), which indicated the increase in the fibrinogen levels was associated with stroke severity.

There was a statistically significant relation between SSS and levels of CRP in the patient group (\(p<0.05\))(\(r=3379\)).

A significant relation between levels of CRP and ferritin within the first 24-72 hours (\(p<0.01\)) was found based on the research results. On the contrary, it was proved that there was no relation between SSS and ferritin values (\(p>0.05\))(\(r=1636\)).

There was a correlation between level of fibrinogen and CRP (\(p<0.05\)), ESR (\(p<0.01\)) (analysis of Pearson correlation). According to this data, increased fibrinogen levels were found to associate with increased CRP and ESR.

STATISTICAL METHODS

The variables found were compared according to values of standard deflection and median values. Median values between groups were determined by using student \(t\) test, Mann-Whitney \(U\), Chi-square, Pearson correlation coefficient, Spearman correlation coefficient and Kruskal-Wallis variant analysis.

DISCUSSION

Atherosclerosis is a response to vessel wall injury, in which many features of an inflammatory process take part (\(1^{11}\)). In other words, there is growing evidence that inflammation plays an important role in the pathophysiology of stroke (\(2^{22}\)). Brain tissue is damaged after acute ischemic stroke, is mediated partly by inflammation induced by ischaemia–reperfusion (I/R) injury. Inflammatory mechanisms contribute to stroke risk via various interrelated mechanisms. The inflammatory parameters such as CRP, fibrinogen or leukocyte counts measured before ischemia are independent predictors of first or recurrent ischemic stroke (\(1^{19}\)).

Fibrinogen is involved in primary hemostasis, platelet aggregation, and leukocyte-endothelial cell interactions and is the major determinant of whole blood and plasma viscosity (\(2^{3}\)). Fibrinogen levels increase after an acute stroke (\(1^{11}\)). In the past, the phenomenon was attributed almost exclusively to an acute-phase reaction due to brain tissue necrosis. However, plasma viscosity and fibrinogen significantly increase in patients with transient ischemic attacks, suggesting that fibrinogen levels are elevated before the stroke (\(1^{12}\)). Similarly, in this study, fibrinogen levels of patient group has been found higher than the control group. There was also difference between the values of first 24 hours and 48-72 hours. Regarding the time, the concentration of fibrinogen increased.

In this study, a positive correlation between SSS and fibrinogen levels in the acute period was observed, which has indicated relation between poor outcome and fibrinogen. Similarly, Cojocaru et al reported that high significant values of
ferritin and CRP, fibrinogen, C3, alpha 1-antitrypsin (AAT), alpha 1-chymotrypsin were observed in patients with poor outcome\(^3\).

Another significant point to be considered here is that genetic predisposition of the inflammatory host response may be an important codeterminant for atherogenesis and stroke risk\(^{17}\). In addition to the genetic factors, for some researchers gender can also be accepted as an important factor in the levels of fibrinogen. For example, Ernest et al reported that women have higher values of fibrinogen than men\(^{11}\). However, in this study, no differences between sexes in terms of fibrinogen concentration (both patient group and control group) were found.

For the patients with acute ischemic stroke, levels of acute phase proteins (CRP, fibrinogen, AAT..) were found high, which suggests that ischemic necrosis is associated with inflammatory reactions\(^2\). Brain ischemia elicits an inflammatory response with a rapid accumulation of granulocytes and later of mononuclear leukocytes around the infarct zone\(^{10}\). In a recent study, increased levels of CRP are reported to be associated with a worse outcome in patients with ischemic stroke\(^6\). Napoli et al reported elevated levels of CRP after ischemic stroke can identify patients with increased risk for disability and mortality\(^5\). Elevated levels of CRP can reflect the extent of brain infarction\(^6,7\).

CRP concentration is an independent predictor of survival after ischemic stroke. These findings are consistent with the role for inflammation in acute ischemic stroke, as well as with the hypothesis that elevated CRP may predict future cardiovascular mortality\(^{21}\). Briefly, the fibrinogen and CRP have a close relationship as inflammatory markers in the acute phase of ischemic stroke\(^{25}\). In this study, which supports the previous ones, it has been found out that CRP levels in the patient were higher than in the control group levels. There is a relation between CRP and SSS. There is higher CRP level in the patients whose clinical health was poor and high SSS.

Studies demonstrate that leukocyte count independently predicts ischemic risk\(^{14,20}\). Leukocytes, including macrophages and lymphocytes, play an important role in the initiation and propagation of the atherosclerotic process\(^8\). In this study, the white blood count in the patients was higher than the controls in the acute period. On the contrary, there was no difference in the ESR values between the two groups.

It is suggested that high serum ferritin levels within the first day of hospitalization for an acute ischemic stroke are related to poor prognosis\(^4\). Oxidative metabolism during ischaemic stroke together with high iron content in the brain synergise to increase the oxidative damage. High plasma ferritin, as a measurement of iron stores, and high cerebrospinal fluid ferritin have been related to poor outcome in stroke patients\(^1\). Serum ferritin level and large size of lesion were independently associated with mortality. Increased serum ferritin levels correlate to severity of stroke and the size of the lesion\(^{13}\).

In this study, concentration of ferritin was higher in the patient group within the first 24-72 hours and is correlated with levels of fibrinogen and CRP. However, there is no relation between ferritin and SSS levels. The levels of ferritin may be different in the stroke subtypes. In this study, the stroke subtypes and the lesion sizes were not determined. Like ferritin, the evaluation of all other parameters via these two tables is undoubtedly significant. Thus, an important question to be asked at this step is that if the results would have changed if the subtypes and the lesion sizes were taken into consideration. In fact, this might be a limitation of this study.

In conclusion, the inflammatory reactions in which acute phase reactants play role, are activated in acute ischemic stroke and generally, this state relates to severity of disease. The results of this study supported
the argument that mainly fibrinogen, ferititin and CRP increase after acute ischemic stroke and they have a close relationship. Decreasing these factors in the acute period (e.g. iron chelating agents, anti-inflammatory agents), may be useful in terms of cerebral injury. Exercise, giving up smoking and clofibrate may decrease fibrinogen levels. Moreover, ancrod has been reported to decrease fibrinogen levels. These parameters will be important to follow both healthy people and patients with stroke in terms of vascular disease in the future.

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