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Serum amyloid A, fetuin-A, and pentraxin-3 levels in patients with ischemic stroke: novel prognostic biomarkers?

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Aim: Inflammation plays an important role in acute ischemic stroke. In this study we aimed to investigate the relationship between acute ischemic stroke and serum amyloid A, fetuin-A, and pentraxin-3 which are inflammation markers.

Materials and methods: We enrolled 52 patients with acute ischemic stroke and 30 sex-matched control subjects in the study. The patients were followed for 3 months. We evaluated the common risk factors, laboratory variables, and neurological examination of stroke patients according to prognosis scales.

Results: The median serum amyloid A, fetuin-A, and pentraxin-3 levels in the stroke patients were higher than in control subjects (respectively, P = 0.000, P = 0.002, and P = 0.037). National Institutes of Health Stroke Scale scores, glucose, C-reactive protein, fibrinogen, and white blood cell count showed differences within the group in terms of the serum amyloid A tertiles statistically.

Conclusion: Pentraxin-3, fetuin-A, and serum amyloid A all arise together as novel prognostic factors in a group of patients with ischemic stroke. Relationships between higher levels of inflammation markers, especially serum amyloid A, and the severity of acute ischemic stroke were shown.

Key words: Serum amyloid A, fetuin-A, pentraxin-3, acute ischemic stroke

1. Introduction

There is a significant contribution of inflammation in the progression of acute ischemic stroke (AIS) (1). Since stroke is a disease with high costs, prediction of the risk for it with an outlook toward the severity of the disease and prognosis is necessary for accurate care and designation of limited health resources (2).

Pentraxin-3 (PTX3) may be a novel, strong, and independent prognostic marker for ischemic stroke (IS). It is a member of the long pentraxins (2). Studies have shown that higher levels of C-reactive protein (CRP), which is a classical short pentraxin, are associated with worsening prognosis of IS (3–5). In acute infections PTX3 plays a protective role by reducing the inflammatory response (6). Especially in acute myocardial infarction, it was shown that the prognostic value of PTX3 was higher than to that provided by troponin T, creatine kinase, CRP, and N-terminal probrain natriuretic peptide (7).

Fetuin-A (α2-Heremans-Schmid glycoprotein) is a circulating serum glycoprotein that is predominantly liver-derived. It is a natural inhibitor of the insulin-stimulated insulin receptor tyrosine kinase. There is also the contribution of subclinical inflammation. Thus, it is shown that plasma fetuin-A levels predict the risk of AIS (8,9).

Serum amyloid A (SAA), which is a multifunctional acute-phase protein, is indicated as a useful biomarker for the confirmation of atherothrombotic ischemic stroke diagnosis. It is synthesized predominantly in the liver (10,11). A strong and independent relationship between SAA and future cardiovascular events has been reported (12).

There were studies about the neuroprotective effect of albumin in IS in humans and animals. Higher albumin levels are found to be associated with better outcome and lower mortality in IS patients (13).

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According to our literature review, novel prognostic factors have been studied individually, but no study has evaluated these factors together in a group of patients. The aim of this study was to measure SAA, PTX3, and fetuin-A levels in patients with AIS to determine any the relationships between serum levels of these factors and prognosis of the disease. We also evaluated other acute phase proteins such as CRP, fibrinogen, and albumin, as well as common risk factors.

2. Materials and methods

2.1. Study population

We enrolled 52 patients with AIS who were admitted to the neurology clinic of Ankara Numune Training and Research Hospital and 30 sex-matched control subjects between January and September 2012. Outpatients who did not have the diagnosis of stroke ever in their lifespan were included as control subjects. We excluded patients or control subjects who had any known infectious, inflammatory, or neoplastic diseases.

The study was approved by the Ethics Committee of Ankara Numune Training and Research Hospital and the study subjects or their relatives gave informed consent for participation in the study.

2.2. Data collection

Patients were questioned for the frequency of stroke attacks and risk factors such as smoking, drinking, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and peripheral arterial disease. Standard laboratory tests, 12-lead electrocardiography, and cranial computerized tomography (CT) were performed on admission. The type of AIS was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) (14): cardioembolic infarct (CEI), large-artery atherosclerosis (LAAS), lacunar infarct (LAC), stroke of undetermined etiology (UDE), and stroke of other determined etiology (ODE). Infarct volumes were measured by CT. The patients were followed for about 3 months. The functional disabilities of patients were measured using the Barthel Index-20 scale (BI-20), the National Institutes of Health Stroke Scale (NIHSS), and the modified Rankin Scale (mRS) in the acute phase and 3 months later (15,16).

2.3. Laboratory analysis

Blood samples were taken from all patients within 24 h. Serum levels of CRP, glucose, and albumin were all measured using the Roche Modular P800 (Roche Diagnostics, Indianapolis, IN, USA), white blood cell (WBC) counts were determined using Sysmex XE-2100 (Sysmex, Kobe, Japan), and fibrinogen levels were analyzed with the STA-Compact Analyzer (Diagnostica Stago-Roche, USA) at the time of admission. For SAA, fetuin-A, and PTX3 measurements, blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA) (Becton Dickinson, Franklin Lakes, NJ, USA) and centrifuged for 10 min at 3000 × *g*. Plasma samples were frozen and stored at –80 °C until the analyses were performed. We measured plasma fetuin-A (BioVendor, Heidelberg, Germany), SAA (Invitrogen, USA), and PTX3 (R&D Systems, USA) by using enzyme-linked immunosorbent assay (ELISA).

2.4. Statistical analysis

Statistical analyses were performed with SPSS 13 (SPSS, Chicago, IL, USA). Normality was measured with the Kolmogorov–Smirnov test. The results were expressed as percentages for categorical variables and as means in normally distributed variables or medians in nonnormally distributed variables. The 2-tailed Mann–Whitney U test was used to compare the median values of parameters in the patient and control groups. The independent-samples t-test was used to compare means. For statistical analyses, the patients were divided into tertiles according to their PTX3, fetuin-A, and SAA levels. The Kruskal–Wallis test was used to compare the median values of parameters in the PTX3, fetuin-A, and SAA tertiles. The level of statistical significance was set at $P < 0.05$.

3. Results

Clinical variables of AIS patients and serum levels of some laboratory parameters of patients and control subjects are shown in Table 1. Plasma fetuin-A, PTX3, and SAA levels were higher in subjects with AIS than the controls ($P = 0.002$, $P = 0.037$, and $P = 0.000$, respectively). Patients with AIS were older than the control subjects. There were no differences in terms of sex between patients and controls. In contrast, differences in smoking reached statistical significance between those with AIS and without AIS. Individuals who developed AIS more often had comorbidities such as diabetes mellitus, hypertension, atrial fibrillation, hyperlipidemia, or coronary artery disease. Two patients died during the follow-up. In these patients, plasma PTX3 levels were 11.60 ng/mL and 43.59 ng/mL, plasma fetuin-A levels were 497.3 μg/mL and 332 μg/mL, and SAA levels were 30.56 μg/mL and 173.31 μg/mL.

Characteristics of patients according to tertiles of PTX3, fetuin-A, and SAA are shown in Tables 2–4. The NIHSS scores, serum glucose, CRP levels, plasma fibrinogen levels, and WBC counts were different according to the SAA tertiles statistically. Only the infarct volume of the third tertile and the WBC count of the second tertile of fetuin-A were higher than other relevant tertiles. However, there were no differences in the clinical or laboratory variables among the tertiles of PTX3 statistically.

Table 1. Clinical variables of acute ischemic stroke (AIS) patients and serum levels of some laboratory variables of patients and control subjects.

	Stroke patients (n = 50)	Control subjects (n = 35)	P
Male, n (%)	21 (67.7)	10 (32.3)	0.175
Mean age, years ± SD	68.2 ± 13.3	62.56 ± 11	**0.021**
Smoking status, n (%)	18 (78.3)	5 (21.7)	**0.022**
Alcohol status, n (%)	3 (100)	0	0.135
Comorbidity, n (%)			
Hypertension	41 (70.7)	17 (29.3)	**0.001**
Atrial fibrillation	12 (24)	0	
Coronary artery disease	22 (81.5)	5 (18.5)	**0.003**
Diabetes mellitus	25 (80.6)	6 (19.4)	**0.001**
Peripheral artery disease	2 (66.7)	1 (33.3)	0.761
Hyperlipidemia	15 (78.9)	4 (21.1)	**0.037**
TOAST, n (%)			
CEI	12 (24)		
LAAS	25 (50)		
LAC	11 (22)		
UDE	2 (4)		
Attacks frequency, 1	41		
Admission NIHSS	7 (5.9)		
Admission MRS	3.5 (2.4)		
NIHSS (after 3 months)	3 (2.5)		
MRS (after 3 months)	2 (1.3)		
Barthel (after 3 months)	97.5 (85.100)		
Infarct volume	343.37 (221.84)		
Pentraxin-3, ng/mL	8.03 ± 6.38	5.53 ± 2.47	**0.037**
Fetuin-A, µg/mL	486.04 ± 85.01	402.72 ± 118.46	**0.002**
Serum amyloid A, µg/mL	134.31 ± 62.15	57.59 ± 54.61	**0.000**

Significant findings ($P < 0.05$) are marked with bold-faced type.
TOAST, Trial of Org 10172 in Acute Stroke Treatment; CEI, cardioembolic infarct; LAAS, large-artery atherosclerosis; LAC, lacunar infarct; UDE, stroke of undetermined etiology; ODE, stroke of other determined etiology; NIHSS, National Institutes of Health Stroke Scale; MRS, modified Rankin Scale.

Table 2. Characteristics of patients according to tertiles of pentraxin-3.

	1 (n = 18)	2 (n = 23)	3 (n = 9)	P
Pentraxin-3, range, ng/mL	1.49–4.41	5.20–10.34	12.35–30.34	
Pentraxin-3, median, ng/mL	3.49	7.02	16.38	
Male, n (%)	9 (50)	7 (30.4)	5 (55.6)	0.31
Mean age, years (SD)	68 (13)	65 (14)	73 (8.5)	0.48
TOAST				0.29
CEI	3 (16.7)	8 (34.8)	1 (11.1)	
LAAS	11 (61.1)	10 (43.5)	4 (44.4)	
LAC	3 (16.7)	4 (17.4)	4 (44.4)	
UDE	1 (5.6)	1 (4.3)	0	
Attacks frequency, 1	14 (77.8)	20 (87.0)	7 (77.8)	0.68
Admission NIHSS	7 (3)	6.5 (7)	7 (5)	0.83
Admission MRS	3.5 (1)	4 (2)	3 (3)	0.52
NIHSS (after 3 months)	3 (3)	3 (3)	2.5 (5)	0.56
MRS (after 3 months)	2 (2)	2 (1)	2 (2)	0.63
Barthel (after 3 months)	95 (48)	95 (19)	100 (10)	0.51
Infarct volume	302.31 (173.40)	385.68 (265.72)	250 (158)*	0.60
Smoking n (%)	8 (44.4)	6 (26.1)	4 (44.4)	0.41
Alcohol status n (%)	2 (11.1)	1 (4.3)	0	0.48
Comorbidity n (%)				
Hypertension	16 (88.9)	17 (73.9)	8 (88.9)	0.40
Atrial fibrillation	5 (27.8)	6 (26.1)	1 (11.1)	0.60
Coronary artery disease	8 (44.4)	11 (47.8)	3 (33.3)	0.76
Diabetes mellitus	7 (38.9)	12 (52.2)	6 (66.7)	0.39
Peripheral artery disease	0	1 (4.3)	1 (11.1)	0.39
Hyperlipidemia	5 (27.8)	6 (26.1)	4 (44.4)	0.58
Glucose (mg/dL)	106 (35)*	132 (42.30)	298 (155)	0.43
CRP (mg/L)	9 (10.98)*	7 (14)*	3 (69.74)*	0.63
Albumin (g/L)	38.84 (5.92)	40 (10)*	38 (4.56)	0.50
Fibrinogen (mg/dL)	474.38 (90.04)	454.23 (112.87)	401.60 (147.49)	0.17
White blood cell (10^3/μL)	9.76 (4.09)	9.58 (3.22)	12.25 (3.91)	0.30

Data are presented as the mean (standard deviation) or *median (interquartile range).
TOAST, Trial of Org 10172 in Acute Stroke Treatment; CEI, cardioembolic infarct; LAAS, large-artery atherosclerosis; LAC, lacunar infarct; UDE, undetermined etiology; ODE, stroke of other determined etiology; NIHSS, National Institutes of Health Stroke Scale; MRS, modified Rankin Scale.

Table 3. Characteristics of patients according to tertiles of fetuin-A.

	1 (n = 19)	2 (n = 16)	3 (n = 14)	P
Fetuin-A, range, μg/mL	131.80–339.3	349.90–436.30	477.50–798.50	
Fetuin-A, median, μg/mL	281.27	394.73	547.91	
Male, n (%)	8 (40)	8 (40)	4 (20)	0.49
Mean age, years (SD)	67 (12.64)	65 (12.93)	65.50 (13.08)	0.62
TOAST				0.87
CEI	4 (33.3)	3 (25)	5 (41.7)	
LAAS	9 (37.5)	10 (41.7)	5 (20.8)	
LAC	6 (54.5)	3 (27.3)	2 (18.2)	
UDE	0	0	2	
Attacks frequency, 1	16 (40)	14(35)	10 (25)	0.54
Admission NIHSS	7.5 (4)	8 (4)	9 (5)	0.42
Admission MRS	4 (1)	4 (1)	4 (1)	0.79
NIHSS (after 3 months)	4 (5)	3.5 (3)	3 (3)	0.53
MRS (after 3 months)	2.5 (2)	2 (1)	2 (3)	0.86
Barthel (after 3 months)	85 (78)	92.5 (34)	92.5 (15)	0.73
Infarct volume	255.92 (212.84)	350 (100)*	367.70 (260.33)	**0.07**
Smoking n (%)	7 (41.2)	5 (29.4)	5 (29.4)	0.94
Alcohol status n (%)	1 (33.3)	2 (66.7)	0	0.36
Comorbidity n (%)				
Hypertension	18 (43.9)	11 (26.8)	12 (29.3)	0.12
Atrial fibrillation	4 (33.3)	3 (25)	5 (41.7)	0.51
Coronary artery disease	7 (31.8)	7 (31.8)	8 (36.4)	0.52
Diabetes mellitus	11 (45.8)	9 (37.5)	4 (16.7)	0.20
Peripheral artery disease	1 (100)	0	0	0.45
Hyperlipidemia	5 (35.7)	6 (42.9)	3 (21.4)	0.61
Glucose (mg/dL)	145 (52.86)	136 (54.58)	114 (38.04)	0.40
CRP (mg/L)	9 (45.00)*	7.67 (12.00)*	5.33 (14.07)*	0.72
Albumin (g/L)	38.25 (4.73)	39.25 (6.28)	38.60 (5.97)	0.59
Fibrinogen (mg/dL)	498.25 (102.60)	434.25 (135.12)	436.66 (93.05)	0.41
White blood cell (10^3/μL)	10.37 (3.70)	12.02 (4.04)	7.79 (2.61)	**0.02**

Data are presented as the mean (standard deviation) or * median (interquartile range).
Significant findings for the differences among tertiles of fetuin-A levels ($P < 0.05$) are marked in bold-faced type.
TOAST, Trial of Org 10172 in Acute Stroke Treatment; CEI, cardioembolic infarct; LAAS, large-artery atherosclerosis; LAC, lacunar infarct; UDE, undetermined etiology; ODE, stroke of other determined etiology; NIHSS, National Institutes of Health Stroke Scale; MRS, modified Rankin Scale.

Table 4. Characteristics of patients according to tertiles of SAA.

	1 (n = 11)	2 (n = 15)	3 (n = 24)	P
SAA, range, μg/mL	11.90–63.01	79.33–168.19	170.23–199.0	
SAA, median, μg/mL	26.55	145.62	184.33	
Male, n (%)	6 (28.6)	6 (28.6)	9 (42.9)	0.63
Mean age, years (SD)	63 (15.03)	64 (14.27)	68.40 (11.08)	0.38
TOAST				0.47
CEI	3 (25)	3 (25)	8 (50)	
LAAS	3 (12)	8 (32)	14 (56)	
LAC	3 (27.3)	4 (36.4)	4 (36.4)	
UDE	2 (100)	0	0	
Attacks frequency, 1	7 (17.1)	14 (34.1)	20 (48.8)	0.17
Admission NIHSS	6.5 (4)	8 (4)	8 (7)	0.11
Admission MRS	4 (1)	3.5 (1)	4 (2)	0.16
NIHSS (after 3 months)	3(3)	2 (2)	4 (4)	**0.02**
MRS (after 3 months)	2 (2)	2 (3)	2 (2)	0.30
Barthel (after 3 months)	100 (81)	90 (33)	90 (60)	0.37
Infarct volume	360.33 (276.48)	271.60 (176.56)	366 (231.71)	0.66
Smoking n (%)	5 (27.8)	7 (38.9)	6 (33.3)	0.30
Alcohol status n (%)	1 (33.3)	1 (33.3)	1 (33.3)	0.85
Comorbidity n (%)				
Hypertension	8 (19.5)	13 (31.7)	20 (48.8)	0.65
Atrial fibrillation	4 (33.3)	3 (25)	5 (41.7)	0.56
Coronary artery disease	5 (22.7)	8 (36.4)	9 (40.9)	0.63
Diabetes mellitus	3 (12)	8 (32)	14 (56)	0.23
Peripheral artery disease	0	0	2 (100)	0.33
Hyperlipidemia	2 (13.3)	5 (33.3)	8 (53.3)	0.63
Glucose (mg/dL)	121.83 (46.60)	117.10 (46.85)	145.10 (48.84)	**0.03**
CRP (mg/L)	6.5 (16.07)*	6 (4.98)	19 (53.34)*	**0.00**
Albumin (g/L)	37.5 (3.94)	40.1 (4.58)	37.70 (6.42)	0.65
Fibrinogen (mg/dL)	397.33 (53.99)	418.96 (65.08)	483.96 (136.46)	**0.02**
White blood cell (10^3/μL)	8.40 (3.45)	8.30 (2.36)	11.52 (3.95)	**0.03**

Data are presented as the mean (standard deviation) or *median (interquartile range).
Significant findings for the differences among tertiles of SAA levels ($P < 0.05$) are marked in bold-faced type.
TOAST, Trial of Org 10172 in Acute Stroke Treatment; CEI, cardioembolic infarct; LAAS, large-artery atherosclerosis; LAC, lacunar infarct; UDE, undetermined etiology; ODE, stroke of other determined etiology; NIHSS, National Institutes of Health Stroke Scale; MRS, modified Rankin Scale.

4. Discussion

Stroke is the most frequent cause of persistent neurological disability since the majority of strokes are ischemic (17). It is the third leading cause of death worldwide (18–20). Clinical and experimental studies suggest that inflammatory mechanisms play an important role in the pathogenesis of IS (18,21). More studies are performed to explain the inflammatory process in AIS and to make better treatment decisions and individualization of therapy nowadays (1,3,22,23). The biochemical parameters used routinely also were used in these studies (21).

PTX3, fetuin-A, and SAA have been studied individually in AIS (2,8,10). Ryu et al. (2) demonstrated that PTX3 was a strong and independent predictor of long-term mortality after AIS.

Weikert et al. (8) showed that plasma fetuin-A levels were associated with the risk of AIS. We found that serum fetuin-A levels were higher in subjects with AIS than in the control subjects. Infarct volume of the third tertile and WBC count of the second tertile of fetuin-A were higher than other relevant tertiles. However, this difference was not statistically significant. One of our exitus patients had high serum fetuin-A levels, but the other exitus patient's fetuin-A level was in the first tertile.

Brea et al. (10) found that high SAA levels predicted atherothrombotic stroke. We also showed that the number of patients with LAAS (n = 14) of the third tertile of SAA was higher than those of other tertiles of it (n = 3, n = 8, respectively) and higher than the third tertile of PTX3 and fetuin-A. The NIHSS scores, serum glucose, CRP levels, plasma fibrinogen levels, and WBC count were statistically different in respect to the SAA tertiles.

Kumar et al. (23) showed that leukocytosis correlated with poor functional outcomes and might represent a marker of greater cerebral damage through increased parenchymal inflammation. We found that infarct volume and WBC count of the second tertile of fetuin-A were higher than in the first tertile.

We did not find differences among serum albumin levels in terms of PTX3, SAA, and fetuin-A tertiles. Kisialiou et al. (22) showed that low-to-normal albumin levels were associated with more extended lesions. According to our study results, higher albumin levels were associated with smaller infarct volumes in the second tertile of SAA, but these differences were not statistically significant.

Studies have shown that CRP was strongly associated with the prognostic outcome after AIS (1,19,24,25). Ormstad et al. (1) found that CRP played an important role in the progression of cerebral tissue injury. We found a significant elevation in CRP only in the third tertile of SAA. The NIHSS scores in the third month of the same tertile of SAA were significantly higher than other tertiles. We thus indicated that elevated CRP levels in the AIS patients were consistent with worse prognoses.

We also established that PTX3, fetuin-A, and especially SAA might arise as novel prognostic markers for IS. This study demonstrated that plasma PTX3, SAA, and fetuin-A levels substantially increased in AIS patients. In particular, the IS patients presenting with the highest SAA-level tertile showed worse prognoses.

There are several important limitations regarding our study. First, we could not obtain samples from many controls to analysis serum glucose, CRP, fibrinogen, WBC count, and albumin levels. We therefore did not compare these levels between patients with AIS and controls. Secondly, our patients were older and had more comorbidities such as hypertension, hyperlipidemia, atrial fibrillation, coronary artery disease, and diabetes mellitus than the control subjects. These factors might act as confounders in our study. We therefore divided patients into tertiles according to the PTX3, fetuin-A, and SAA levels and compared the median values of parameters, especially prognostic scores, in the PTX3, fetuin-A, and SAA tertiles. This situation caused a reduction in the number of patients. To our knowledge, this was the first study that evaluated these factors in a group of patients. Larger population-based studies are needed to confirm our results. Another limitation of our study was that our results were based on single blood samples for measurements of PTX3, SAA, and fetuin-A, which might have introduced random measurement errors in determining biochemical variables.

In light of the findings obtained from the present study, it may be assumed that increased SAA observed in AIS patients appears to be related to worse prognoses and to inflammatory conditions in these patients, and may cause much more severe manifestation of the disease.

One result of this study is that reducing serum levels of SAA and some inflammatory markers might be beneficial for patients with AIS. However, further studies are needed to clarify the release of other inflammatory markers than the usual known ones in AIS and their relationships with progression of neurological injury.

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