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Diagnostic Value of Pentraxin-3 in Patients with Spontaneous Subarachnoid and Intracerebral Hemorrhage

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Abstract

Aim: In this study, the diagnostic and prognostic values of serum pentraxin-3 (PTX3) level were evaluated in spontaneous subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH) patients.

Materials and Methods: The study was conducted prospectively on patients in the emergency department between April 2014 and December 2015 at the Faculty of Medicine. Patients who were older than 18 years, who presented to the emergency department with neurologic findings, and who were diagnosed with SAH and ICH pursuant to a computed tomography (CT) scan of the brain were included. PTX3 levels were evaluated in the blood samples collected at the time of presentation to hospital and at the twelfth hour after presentation.

Results: In the study, the levels of serum PTX3 measured at presentation and at the twelfth hour after presentation were found to be statistically and significantly different in the SAH group compared to the control group ($p<0.001$; $p<0.001$, respectively). Serum PTX3 levels measured at presentation and at the twelfth hour after presentation were found to be significantly different in the ICH group compared to the control group ($p<0.001$; $p<0.001$, respectively).

Conclusion: The study findings show that measuring serum PTX3 levels in SAH and ICH patients may be an adjuvant test. We consider that this finding should be supported by comprehensive and controlled studies.

Keywords: Spontaneous subarachnoid hemorrhage, intracerebral hemorrhage, pentraxin-3

Introduction

Intracerebral hemorrhage (ICH), like subarachnoid hemorrhage (SAH), has high mortality and morbidity risk. In primer ICH patients, advanced age, place and size of hemorrhage, whether or not it is opened to the ventricle are related to mortality and morbidity (1).

Pentraxins are acute phase proteins in multimeric form (2). They are classified as long or short pentraxins, according to their structures. Pentraxin-3 (PTX3) is a prototype of the long pentraxins. C-reactive protein (CRP) is produced in the liver as a primer by IL-6. During a systemic response to local inflammation, PTX3 is directly released from damaged tissue, reflecting the inflammatory situation of the vascular structure (3). Therefore, in vascular pathologies, the level

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of plasma PTX3 may be increased. This increase may contribute to the determination of diagnosis and prognosis of vascular pathology.

Materials and Methods

The study was a prospective clinical study and was initiated after approval of the local clinical research ethics committee. Patients who presented to emergency department in the university hospital with a suspicion of neurologic disease between April 2014 and December 2015, who were diagnosed with SAH or ICH, and who were over 18 years of age were included in the study. Patients with acute renal failure, chronic renal failure, sepsis, hepatic insufficiency, acute pulmonary edema, peripheral artery disease, deep vein thrombosis, acute coronary syndrome, pulmonary embolism, mesenteric ischemia, cardiac arrest, multitrauma, puerperality, hemorrhage due to tissue plasminogen activator (TPA), or patients who were pregnant and who, either personally or through their relatives, did not provide consent to participate in the study were excluded from the study. Blood samples were collected from patients at the time of presentation and at the twelfth hour after presentation. Healthy volunteers aged >18 years, with no disease, and who presented to hospital for check-up were admitted to the study as control group, after obtaining their consent.

At the time of presentation, to measure the levels of PTX3, serum samples were collected in CBC tubes containing ethylene diamine tetra acetic acid (EDTA). Plasma was separated by centrifugation at 1800×g for 10 min and stored at −80°C until the PTX3 study.

Determination of PTX3 levels in human plasma

PTX-3 levels in human plasma were determined using enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Cat No: DPTX30, Lot: 334734, Minneapolis, USA) in accordance with the manufacturer's recommendations. PTX-3 levels in samples were calculated in ng/mL.

Statistical analysis

For statistical analysis of the study, Statistical Package for Social Sciences (SPSS Inc.; Chicago, IL, USA) for Windows version 13.0 software was used. The expression of values of control and patient groups; categorical variables were expressed as percentage; quantitative variables were expressed as average and standard deviation (X±SD) if they comply with normal distribution and as mean and interquartile percentages if they do not comply with normal distribution. During comparison of averages among groups, the Kruskal–Wallis test was used for data that do not comply with normal distribution. To determine among in groups this difference occurs, Mann–Whitney U test with Bonferroni's correction was used. Spearman correlation analysis was used to determine how a variable is affected as another variable changes. Results were presented as 95% confidence interval (CI) and a p value of <0.05 was considered statistically significant.

Results

In this study, 30 SAH, 49 ICH, and 50 control group patients were included. Of the SAH patients, 40% were over 65 years of age, and 27% were under 45 years of age. Of the ICH patients, 38.7% were over 65 years of age, and 12.2% were under 45 years of age. Females constituted 53% of the SAH group, and males constituted 59% of the ICH patients. Of the control group, 2% were over 65 years of age, 56% were under 45 years of age, and 76% were males. For the SAH patients, mean systolic blood pressure was 155 mmHg and diastolic blood pressure was 86 mmHg; for the ICH patients, mean systolic blood pressure was 185 mmHg and diastolic blood pressure was 98 mmHg. PTX3 values at the time of presentation and at the twelfth hour for the SAH, ICH, and control groups are shown in Figures 1 and 2 as box plots.

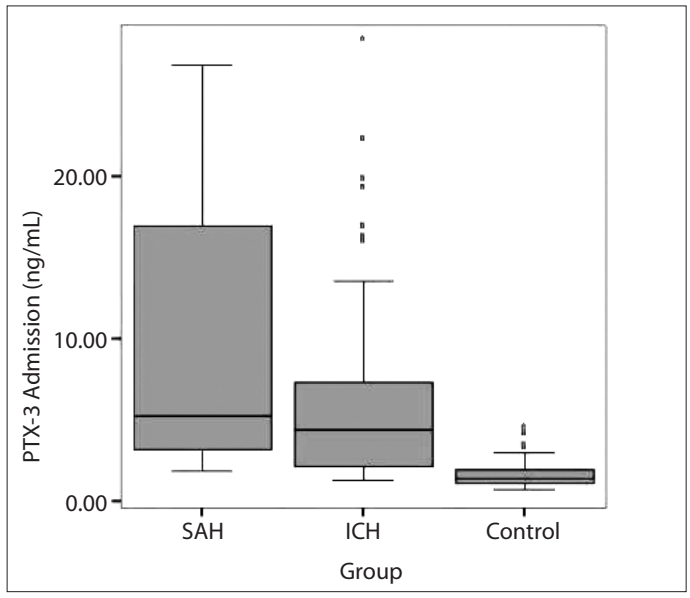

Figure 1. PTX3 values of SAH, ICH, and control groups at the time of presentation

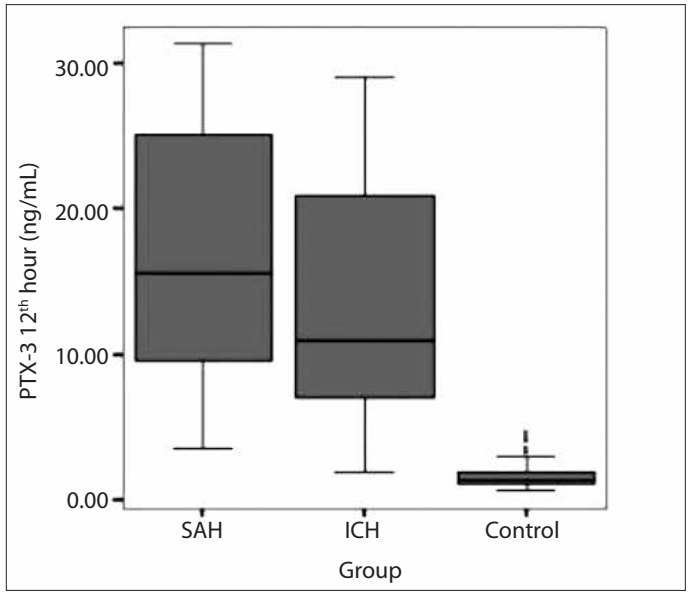

Figure 2. PTX3 values of SAH, ICH, and control groups at the twelfth hour after presentation

The levels of serum PTX3 measured at presentation and at the twelfth hour after presentation were found to be significantly different in the SAH group compared to control group ($p<0.001$; $p<0.001$, respectively). PTX3 median values of the SAH and control group and their comparison are shown in Table 1.

The levels of serum PTX3 measured at presentation and at the twelfth hour after presentation were found to be significantly dif-

Table 1. PTX3 median values of the SAH and control groups and their comparison

	Control	SAH at presentation	SAH at the twelfth hour
PTX3	1.40 (1.11–1.91)[a, b]	5.20 (3.19–17.57)[a, c]	15.60 (9.23–26.41)[b, c]

*Values were given as median (25%-75 %) ng/mL. **For PTX3, [a]: p<0.001; [b]: p<0.001; [c]: p<0.001. SAH: Subarachnoid hemorrhage; PTX3: Pentraxin-3

Table 2. PTX3 median values of the ICH and control groups and their comparison

	Control	ICH at presentation	ICH at the twelfth hour
PTX3	1.40 (1.11–1.91)[a, b]	4.39 (2.14–8.40)[a, c]	11.00 (7.05–21.06)[b, c]

*Values were given as median (25%-75%) ng/mL. **For PTX3, [a]: p<0.001; [b]: p<0.001; [c]: p<0.001. ICH: Intracerebral hemorrhage; PTX3: Pentraxin-3

ferent in the ICH group compared to the control group (p<0.001; p<0.001). PTX3 median values of the ICH and control groups and their comparison are shown in Table 2.

No significant difference could be detected for PTX3 mean values among the SAH and ICH patients at the time of presentation and at the twelfth hour after presentation (p>0.05). To determine prognostic value of the level of PTX3 in the SAH and ICH patients, the levels of PTX3 were compared in living and deceased patients. The levels of PTX3 at the twelfth hour after presentation were detected to be significantly higher for deceased patients in the SAH group compared with the living patients (p<0.05). The AUC in the ROC analysis was 0.623, and if PTX3 cut off was considered 28.04 ng/mL, we may determine decease by 14.8% sensitivity and 95.1% specificity. For the ICH patients, no significant difference could be detected for the levels of PTX3 at the time of presentation and at the twelfth hour after presentation (p>0.05).

Discussion

Seventy-five percent of subarachnoid hemorrhages develop due to ruptured aneurysm (1). The prevalence of aneurysmal SAH increases between 50 and 70 year of age. In some studies, SAH was observed to be more prevalent in females (4, 5). The most important risk factors leading to development of ICH are advanced age and acute or chronic hypertension (6). The risk of ICH increases with age (7); 72%–81% of ICH patients have history of hypertension (8). The patient population of our study resembles that in literature, and it was found that of the SAH patients, 40% were over 65 years of age and 53% were females; of the ICH patients, 38.7% were over 65 years of age and 59% were males. The factors determining mortality in SAH patients include severe neurologic presentation, advanced age, the large size of aneurysm, and the presence of intraparenchymal hemotoma in the first 24 hours (9, 10). Moreover, 12% of patients with SAH due to aneurysm die before hospital arrival, and 25% of patients die in the first 24 hours (11). Similar to SAH, ICH has high mortality and morbidity risk. Deterioration in the clinical picture is very common during the first few hours after the onset of ICH (12). Rapid diagnosis and determination of prognosis in SAH and ICH, where mortality is very high, is crucial for the determination of mortality and morbidity. At the same time, while dealing with severe pathologies, such as SAH and ICH, it is very important for treating physicians to provide realistic responses to questions and expectations of patients and patient relatives. Therefore, accessing biochemical data that may be correlated to patients plays an important role for early diagnosis.

Pentraxins are multifunctional protein superfamily playing role in inflammatory response (13). PTX3 is proven to increase during sepsis and several infective pathologies, and its increase is correlated to the severity of these pathologies (14). Furthermore, it was detected that the level of plasma PTX3 is increased in pathologies, such as ischemic heart diseases, small vessel vasculitis, and pulmonary contussion, where inflammation plays an important role, and that it is correlated to disease activity (15, 16). PTX3 is produced by inflammatory cytokines, such as toll-like receptor (TLR) agonists, interleukin (IL)-1β and tumor necrosis factor (TNF)-α (13). Myeloid dendritic cells, monocytes, macrophages, vascular endothelial cells, smooth muscle cells, kidney epithelial cells, fibroblasts, adipocytes, glial cells, cumulus ophorus cells, mesenchymal cells, and synovial cells are involved in PTX3 production (17). Vascular endothelial and smooth muscle cells produce PTX3 in response to signals containing oxidized low-density cholesterol (LDL), and they are released directly from damaged tissue, which reflects the inflammatory situation of the vascular structure (3, 18). SAH and ICH are cerebrovascular events, and we may suppose that they increase the level of PTX3. It is known that the basal level of PTX3 in circulation is <2 ng/mL; however, during inflammation, the level in circulation may peak within 6 or 8 hours by 3-5 fold of its basal level (17, 19). The mean value of PTX3 in the control group was 1.40 ng/mL, and PTX3 values at the time of presentation were detected to be 4.39 ng/mL in the ICH group and 5.20 ng/mL in the SAH group. The levels of PTX3 in SAH and ICH patients were detected to be significantly higher both at the time of presentation and at the twelfth hour after presentation compared to the control group (p<0.001; p<0.001, respectively). The higher level of PTX3 at the twelfth hour compared to that at the time of presentation shows that PTX3 has the tendency to increase from the onset of the event. In their study, Ryu et al. (20) detected that for ischemic stroke patients, the level of PTX3 at the time of presentation is higher in deceased patients compared to living patients. Zanier et al. (21) showed that the level of PTX3 reached its highest in plasma and cerebrospinal fluid (CSF) samples in SAH patients during first 48 hours and during development of vasospasm. In our study, it was detected that the levels of PTX3 at the twelfth hour after presentation were statistically and significantly higher in deceased patients compared to living patients of the SAH group (p<0.05). No significant difference could be detected for the levels of PTX3 at the twelfth hour of presentation among deceased or living patients of the ICH group (p>0.05). We may consider that the abundance of damage on aneurysmal vascular tissue and development of vasospasm together with creation of a stronger immune response may be the reason for this difference in SAH patients.

Study limitations

The first limitation of this study was that relatively low number of patients were admitted to the study and that control group bears no resemblance with other groups in terms of age and gender. SAH and ICH are conditions that require long-term treatment in the hospital, and we consider that infections during the treatment may affect the levels of serum PTX3. Moreover, the determination of levels of PTX3 of SAH and ICH patients was performed according to the presentation time to emergency department rather than the time of hemorrhage, thus limiting the study.

Conclusion

Subarachnoid hemorrhage and ICH are clinical situations that have very high mortality and morbidity levels if they are not diagnosed. Presence of diagnostic and prognostic biomarkers that are easily accessed and provide results rapidly might relatively reduce the poor prognosis. Pursuant to the results obtained from this study, we may conclude that the measurement of serum PTX3 levels, which is an inflammatory biomarker, may be used as an additional diagnostic test for SAH and ICH. This study must be supported by studies that more comprehensive.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Karadeniz Technical University Scientific Research.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

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