



Research Article

Pregnancy-Associated Plasma Protein A and High-Sensitive C-Reactive Protein Levels in Chronic Subdural Haematoma Patients

Hakan HANIMOĞLU², Mustafa Onur ULU¹, Huseyin BIÇEROĞLU², Ramazan MEMISOGULLARI³, Abdurrahman COŞKUN⁴, Naci BALAK⁵, Merih İŞ⁶, Ercan TÜRECİ⁷, İlhan ELMACI⁵, Mustafa UZAN²

¹Sakarya ToyotaSA State Hospital, Department of Neurosurgery, Sakarya, Türkiye ²Istanbul University, Cerrahpasa Medical Faculty, Department of Neurosurgery, Istanbul, Türkiye ³Düzce University, Medical Faculty, Department of Biochemistry, Düzce, Türkiye ⁴Acıbadem University, Department of Biochemistry, Istanbul, Türkiye ⁵Göztepe Education and Research Hospital, Department of Neurosurgery, Istanbul, Türkiye ⁶Düzce University, Medical Faculty, Department of Neurosurgery, Düzce, Türkiye ⁷Istanbul University, Cerrahpasa Medical Faculty, Department of Anesthesiology and Reanimation, Istanbul, Türkiye

Summary

Objective: Pregnancy-associated plasma protein A (PAPP-A), a metalloproteinase that regulates insulinlike growth factor-1 bioavailability in vitro, has been suggested to play an active role in the pathophysiology of several conditions involving inflammatory responses. We investigated the values of PAPP-A and high sensitive CRP (hsCRP) levels in chronic subdural haematoma (CSDH) patients and healthy controls.

Methods: PAPP-A and hsCRP levels were studied in the serum and subdural haematoma fluid of 20 consecutive patients with CSDHs (M / F: 12 / 8; mean age of 56.7) and in the serum of age matched 16 volunteers (M / F: 10 / 6; mean age: 54,2).

Results: The serum PAPP-A [4.15 ng/mL (2.70-12.88)] levels of patients were significantly lower than control group [9.32 ng/mL (6.57 – 17.00)] ($p < 0.01$) and the hsCRP levels were significantly higher in patient group [4.57 mg/L (1.56 -12.62)] ($p < 0.01$). The comparison of PAPP-A values in the serum and subdural haematoma in the patient group revealed significantly very high values in the subdural fluid [204.5 ng/mL (161.1 – 261.4)] than the serum [4.15 ng/mL (2.70-12.88)] ($p < 0.0001$). The hsCRP values, on the other hand, were significantly lower in the subdural haematoma fluid than the serum in the patient group ($p = 0.016$).

Conclusion: PAPP-A may have an important function in the local inflammatory events and local structural changes associated with CSDH formation and growth. The detection of high peripheral hsCRP levels in the patient group suggests that a systemic inflammatory response follows after the traumatic insult leading to CSDH formation.

Key words: Chronic subdural haematoma, hsCRP, inflammation, PAPP-A, pathophysiology, Pregnancy-associated plasma protein A

Kronik Subdural Hematomlu Hastalarda Gebelik İlişkili Plazma Proteini-A ve Yüksek Duyarlı C-Reaktif Protein Düzeyleri

Özet

Amaç: In vitro koşullarda insulin benzeri büyüme faktörü-1 biyoaktivitesini düzenleyen bir metalloproteinaz olan Gebelik ilişkili plazma proteini-A'nın (PAPP-A), inflammatuar yanıt içeren birçok durumun patofizyolojisinde rol oynadığı bildirilmiştir. Bu çalışmada kronik subdural hematomlu (KSDH) hastalar ve sağlıklı kontrollerdeki PAPP-A ve yüksek duyarlı CRP (hsCRP) düzeylerini araştırdık.

Metod: KSDH'lı 20 ardışık hastanın (E/K: 12/8; ortalama yaş 56.7) serum ve subdural hematom sıvısında ve yaş uyumlu 16 sağlıklı gönüllünün (E/K: 10/6; ortalama yaş 54.2) serumunda PAPP-A ve hsCRP düzeyleri araştırılmıştır.

Bulgular: Hasta grubunun serum PAPP-A düzeyleri [4.15 ng/mL (2.70-12.88)] kontrol grubuna göre [9.32 ng/mL (6.57 – 17.00)] anlamlı olarak düşüktü ($p < 0.01$) ve hasta grubunun hsCRP düzeyleri de [4.57 mg/L (1.56 -12.62)] anlamlı olarak daha yüksekti ($p < 0.01$). Hasta grubunun serum ve subdural hematom sıvısı PAPP-A düzeyleri karşılaştırıldığında subdural hematom sıvısında PAPP-A anlamlı olarak çok yüksek değerlerdeydi [204.5 ng/mL (161.1 – 261.4)] karşı [4.15 ng/mL (2.70-12.88)] ($p < 0.0001$). Buna karşın hasta grubunda hsCRP düzeyleri subdural hematom sıvısında seruma göre anlamlı olarak düşüktü ($p = 0.016$).

Sonuç: PAPP-A'nın KSDH oluşumu ve büyümesi ile ilgili lokal inflammatuar olaylarda önemli görevleri olabilir. Hasta grubunda serumda hsCRP düzeylerinin yüksek olması KSDH oluşumuna yol açan travmatik olay sonrası sistemik bir inflammatuar yanıtın geliştiğini düşündürmektedir.

Anahtar Kelimeler: Kronik subdural hematom, hsCRP, inflamasyon, PAPP-A, patofizyoloji, Gebelik ilişkili plazma proteini-A

INTRODUCTION

Pregnancy-associated plasma protein-A (PAPP-A) was originally isolated as one of four proteins of placental origin found circulating at high concentrations in the serum of pregnant women as reported in 1974⁽¹⁷⁾. There is increasing evidence of a relationship between PAPP-A and inflammation and the current literature suggests that PAPP-A should no longer be considered just “pregnancy-associated”^(2-5,19,23,24). It has been shown that PAPP-A cleaves IGF-binding protein-4 (IGFBP-4) and increase the bioavailability of insulinlike growth factor-1 (IGF-I)^(1,16) which promotes macrophage activation, chemotaxis, and release of pro-inflammatory cytokines and LDL-cholesterol uptake by these cells^(12,22). Increases in PAPP-A expression have been shown to be associated with healing human skin⁽²⁾, neointimal hyperplasia following vascular injury⁽²⁴⁾, normal fracture healing process⁽¹⁹⁾, allergic rhinitis⁽¹⁰⁾, and

asthma⁽³⁾, all of which are associated with inflammatory responses.

The underlying mechanisms regarding the pathophysiology of chronic subdural haematoma (CSDH) have not been elucidated and numerous factors have been claimed to be associated with its formation and growth. Among these factors, inflammatory reactions have been suggested to play important roles in this process^(6,25,28). Several lines of evidence indicated that the inflammation is confined to the subdural haematoma with normal serum levels of C-reactive protein (CRP) and in recent studies, local elevations of inflammatory cytokines such as interleukin-1-beta (IL-1 β), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF- α), bradykinin and platelet-activating factor (PAF) have been detected in the subdural fluids of CSDH patients^(6,11,15,25,26,28). It has been demonstrated that this local response

causes neovascularisation of the outer membrane of CSDH with proliferation of fibroblasts and immature capillaries accompanied by increased vascular permeability^(9,26,27) which in turn causes enlargement of the haematoma.

Based on the hypothesis that inflammation and PAPP-A might have roles in CSDH formation we investigated the values of PAPP-A and high sensitive CRP (hsCRP) levels in CSDH patients and healthy controls.

MATERIAL AND METHODS

We conducted a prospective clinical study among the patients harbouring CSDHs who admitted to the three different neurosurgery departments between December 2007 and October 2008. The patients using antiplatelets, anticoagulants, anti-inflammatory drugs and those with concomitant infective, inflammatory, hematological, neoplastic disease or chronic liver or renal disfunction were excluded from this study. Twenty consecutive patients (male/female: 12 / 8) with a mean age of 56.7 harbouring CSDHs were studied. The diagnoses were based on computerized tomography and/or magnetic resonance imaging. Surgical treatment was performed by irrigating the haematoma cavity via single or double burrholes or a small craniotomy with closed subdural drainage in all cases. Blood samples were collected directly from the CSDH and from the antecubital vein simultaneously at the time of surgical treatment. Peripheral blood control samples were taken from age matched 16 volunteers (M / F: 10 / 6; mean age: 54,2) who also did not possess the same exclusion criterias. Both the patient and the control groups were provided informed consent. All patients were followed up for 6 or more months (mean 7.2 months) and there were no recurrences after the primary surgery.

Measurement of PAPP-A and hsCRP

All samples were collected in sterile tubes without additives and centrifuged at 1500 x g for 10 min in 1 hour. Following centrifugation, the serum aliquots were stored at -20 0C until analysis. All samples were processed within 2 months. Serum PAPP-A levels were determined by an ultrasensitive enzyme-linked immunosorbent assay (ELISA) (DRG Instruments GmbH, Germany) based on sandwich principle. The analytical sensitivity of the method was 0.023 ng/mL and the coefficient of variation (CV) was 6.86%. Serum hsCRP levels were measured by chemiluminescent enzyme immunoassay (Immulite 1000, DPC Diagnostics, Los Angeles, CA, USA) with intra-assay CV of 5% and a sensitivity of 0.1 mg/L.

Statistical Analysis

Data are expressed as median and interquartile range. The Anderson-Darling normality test was used to evaluate the normality of the data. The Mann-Whitney U-test were used to evaluate the significance of differences between the control and CSDH groups. Differences in the values of PAPP-A and hsCRP levels of peripheral blood and subdural haematoma in the CSDH group were further evaluated by using Wilcoxon signed-ranks test. Correlations between variables were assessed using Spearman correlation analysis. Values of $p < 0.05$ were considered as statistically significant.

RESULTS

The demographic features, PAPP-A and hsCRP levels in patient and control groups are summarized in Table 1. As shown in Table 2, the serum PAPP-A levels of patients [4.15 ng/mL (2.70-12.88)] were significantly lower than control group [9.32 ng/mL (6.57-17.00)] ($p < 0.01$). In contrast to PAPP-A, hsCRP levels were significantly higher in patient group [4.57 mg/L (1.56-12.62)] than the controls [1.56 mg/L (0.81-2.66)] ($p < 0.01$). The comparison of PAPP-A values in the serum and subdural haematoma in the

patient group revealed significantly very high values in the subdural fluid [204.5 ng/mL (161.1-261.4)] than the serum [4.15 ng/mL (2.70-12.88)] ($p < 0.0001$) (Figure 1). The hsCRP values, on the other hand, were significantly lower in the subdural

haematoma fluid [1.49 mg/L (0.83-5.83)] than the serum [4.57 mg/L (1.56-12.62)] in the patient group ($p = 0.001$). We did not find any significant correlation between PAPP-A and hsCRP in patient and control groups ($p > 0.05$).

Table 1. The demographic features, PAPP-A and hsCRP levels in patient and control groups.

Patient #	Age / Sex	PAPP-A SDH	PAPP-A S	hsCRP SDH	hsCRP S	Control #	Age / Sex	PAPP-A S	hsCRP S
1	73 / M	157	57,5	0,96	3,11	1	63 / M	8,73	0,46
2	63 / F	567,5	2,65	1,89	4,68	2	50 / F	5,45	0,78
3	50 / M	247,5	4,75	0,91	4,46	3	48 / F	6,39	8,43
4	61 / M	266	1,95	0,793	12,3	4	59 / M	20,93	0,84
5	49 / M	134,5	3,1	1,12	0,611	5	51 / M	4,74	1,53
6	55 / F	178,5	2,4	0,44	12,7	6	44 / F	17,41	0,8
7	57 / M	175	28,65	2,4	13,4	7	58 / M	12,48	24,7
8	42 / M	230	83,3	0,81	11,4	8	55 / F	8,03	2,23
9	53 / M	236	57,6	2,74	2,94	9	58 / M	9,2	2,8
10	47 / F	3,8	5,7	0,787	0,539	10	43 / M	6,12	1,3
11	68 / F	84	6,15	6,72	7,92	11	51 / M	13,89	3,21
12	56 / M	198	2,85	13,2	14	12	62 / F	9,44	1,59
13	50 / F	220,5	3,35	12,8	14	13	50 / M	15,77	1,19
14	56 / F	173,5	2,15	0,417	1,45	14	53 / M	7,09	1,58
15	61 / F	680,5	2,4	1,85	12,4	15	66 / M	27,03	2,24
16	72 / M	192,5	3,55	3,13	1,88	16	57 / F	23,74	0,3
17	56 / M	310	14,8	0,997	1				
18	48 / M	87	3,35	76,7	0,486				
19	59 / F	304	7,1	17	61,8				
20	59 / M	211	5,9	0,9	2,75				

Abbreviations: S: Serum; SDH: Subdural haematoma. PAPP-A and hsCRP values are expressed in (ng/mL) and (mg/L) respectively.

Table 2. The comparisons of serum PAPP-A and hsCRP values among both groups and serum and subdural values in CSDH group.

	CSDH	Control	P value ‡
PAPP-A S	4.15 (2.70 - 12.88)	9.32 (6.57 - 17.0)	0.001
hsCRP S	4.57 (1.56 - 12.62)	1.56 (0.81 - 2.66)	0.001
	CSDH		
	SDH	S	P value †
PAPP-A	204.5 (161.1 - 261.4)	4.15 (2.70 - 12.88)	0.001
hsCRP	1.49 (0.83 - 5.83)	4.57 (1.56 - 12.62)	0.001

Abbreviations: S: Serum; SDH: Subdural haematoma. PAPP-A and hsCRP values are expressed in (ng/mL) and (mg/L) respectively. All values are expressed as the mean $\pm$ SD. ‡: Mann Whitney U test; †: Wilcoxon Signed Rank Test

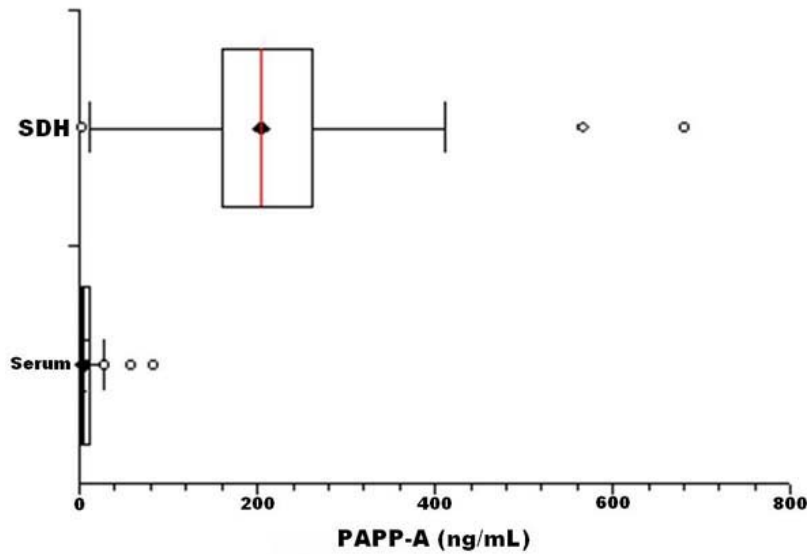


Figure 1: PAPP-A levels in serum and subdural haematoma in the patient group.

Abbreviations: SDH: Subdural haematoma

DISCUSSION

The present study, aimed to investigate whether PAPP-A has a role in the CSDH pathophysiology or not and to the best of our knowledge, is the first one carried among CSDH patients. According our results, the median serum hsCRP levels were found to be significantly higher in the patient group than the controls, suggesting that a systemic inflammatory response follows after the traumatic insult leading to CSDH formation. The finding of decreased peripheral blood PAPP-A levels in the patient group than the controls suggests that PAPP-A does not have a systemic effect in CSDH pathophysiology. However, it also cannot be excluded that the time interval between the initial trauma and surgical haematoma evacuation may also have influenced the PAPP-A levels. The detection of significantly high PAPP-A levels in the subdural haematoma than the serum in the patient group raises the possibility that PAPP-A may have important roles in the chronic/healing phase of CSDH pathophysiology rather than the acute phase. The production of

excessive levels of PAPP-A and its release into the haematoma appear to be linked to the local structural changes occurring within the subdural haematoma cavity. We can conclude that rises in the PAPP-A levels may be critical in the degradation of IGFBP-4, which in turn amplify local IGF-I activity.

The metzincin metalloproteinase PAPP-A, has recently been shown to cleave IGFBP-4 which generally function to antagonize the activity of IGF-I⁽¹⁾. This specific function, which potentially increases the bioavailability of IGF-I⁽¹⁶⁾, is believed to be involved in a number of physiological and pathological processes known to involve IGF signaling such as wound healing and tissue and bone remodeling^(1,2). Its' role in vascular injury and repair process has been shown to contribute to the progression of both coronary atherosclerosis and restenosis⁽¹⁴⁾. Increases in PAPP-A expression have also been shown to be associated with healing human skin and neointimal hyperplasia following vascular injury^(2,24). In a study by Miller et al. PAPP-A knock-out mice showed

marked delay in fracture healing compared with wild-type mice⁽¹⁹⁾. The authors suggested that PAPP-A is necessary in the early phases of the process for expeditious fracture repair and the ability of PAPP-A to enhance local IGF action may be an important mechanism for optimizing the fracture repair response⁽¹⁹⁾. The findings in the present study may reflect the role of PAPP-A in the injury/repair response in CSDH, similar to the previous reports investigating PAPP-A's role in wound healing and inflammation on different pathologies^(2-5,19,23,24).

The inflammatory markers have been studied extensively in the pathophysiology of CSDH and several authors have reported that different direct or indirect inflammatory markers such as fibrinogen degradation products, platelet-activating factor, VEGF, bradykinin, tissue plasminogen activator, IL-6, IL-8, and tumor necrosis factor are present at a higher concentration in a haematoma than in serum^(6-9,11,13,18,20,21,25,26). Hence, according to the pertinent literature, CSDH is a chronic self-perpetuating local inflammatory process involving a remittent cycle of angiogenesis, increased vascular permeability, hypercoagulation and hyperfibrinolysis^(6-9,11,13,18,20,21,25,26) and it has been proposed that this cascade of events beginning after trauma, results in a rebleeding-healing cycle which leads to haematoma progression. hsCRP, playing an important role in acute as well as in chronic inflammation, is one of the most widely used inflammatory markers because of its high level of accuracy and its availability. In this study the peripheral hsCRP levels were found to be significantly higher in the patient group than the controls. This result suggests that systemic inflammatory response play a role in CSDH pathophysiology which probably precedes the local structural changes in CSDH formation. However we acknowledge that, this finding must be supported by evaluating the proinflammatory and inflammatory

cytokines such as IL-6, IL-8...etc in future studies enrolling larger patient populations.

In conclusion, subdural PAPP-A levels are increased in CSDH patients indicating that PAPP-A, as an IGFBP-4 specific metalloproteinase, may have an important role in the injury/repair responses, local inflammatory events and structural changes associated with CSDH formation and growth. The detection of high peripheral hsCRP levels in the patient group suggests that a systemic inflammatory response follows after the traumatic insult leading to CSDH formation. However, future studies with larger population of patients are required to elucidate the exact role(s) of PAPP-A and are to state whether treatment targeting to decrease its activity have beneficial effects on patient's survival.

Correspondence to:

Mustafa Onur Ulu

E-mail: dronurulu@gmail.com

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