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RESEARCH ARTICLE

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The relationship between levels of plasma-soluble urokinase plasminogen activator receptor (suPAR) and presence of migraine attack and aura

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ABSTRACT

Migraine is one of the most common types of pain associated with sterile inflammatory conditions. Soluble urokinase plasminogen activator receptor (suPAR) is a potential novel inflammatory marker. We aim to determine the association between serum values of suPAR, procalcitonin, fibrinogen, and high-sensitivity C-reactive protein (hs-CRP) and migraine disease characteristics. The study involved a total of 60 migraine patients (33 patients in the interictal period, 27 patients in the attack period) and 30 healthy individuals. The serum values of suPAR were found to be significantly higher in migraine patients in the attack period than in migraine patients in the interictal period, and in healthy individuals ($p < .01$ for both). In addition, levels of suPAR were determined to be higher in migraine with aura patients than in migraine without aura patients. When we subdivided migraine patients according to frequency of attack (attacks/month), significant differences were found between the suPAR and procalcitonin levels (measured during the attack period) of those in the frequent-attack group (4–5 or more) versus those in the less frequent attack group (less than 4). Serum levels of procalcitonin were shown to be significantly higher in migraine patients during the attack period compared with migraine patients in the interictal period and in control subjects ($p = .001$ for both). Significant differences were found between plasma levels of fibrinogen in migraine patients versus control subjects ($p < .01$). No statistically significant difference was found between levels of hs-CRP in migraine patients versus the control group. These findings may show that presenting a high level of suPAR in migraine patients with attack and aura results to predisposition to occurring on the symptoms and that high levels of suPAR, procalcitonin and fibrinogen in patients with migraine result in neurogenic inflammation during migraine headaches.

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Migraine; suPAR; procalcitonin; fibrinogen; hsCRP

Introduction

Migraine headache is a serious and also common health problem, affecting between 11.7% and 16.6% of the global population (1). Migraine contributes to decreased quality of life. It is a neurovascular disease characterized by sterile vascular inflammation leading to attacks and remittent periods of headache that may be accompanied by numerous other symptoms (2,3). The etiopathology of migraine is only partly known but is admitted to be occurred through activation of the trigeminovascular system which leads in vasodilation of presenting inflammation by pain-producing intracranial vascular endothelial cells (4). Inflammation may correlate clinically, proving valuable in improved treatment strategy. The International Headache Society (IHS) classifies migraines into two types: migraine with aura and without aura. Several studies have been done that emphasize the factors that cause attacks and the clinical symptoms of migraine (5,6). However, the attack-triggering mechanism has not been precisely identified. There are still no properly recognized laboratory parameters for determining the clinical course of the disease, despite the fact that migraine may result in increased risk of stroke and other thromboembolic events. Further study of the role of thrombosis in a proportion of patients with migraine is warranted.

Urokinase-type plasminogen activator receptor (uPAR) is a glycosyl-phosphatidylinositol-anchored membrane glycoprotein commonly expressed by endothelial cells and in the formation of extracellular tissue (7). uPAR is a valuable component of the fibrinolytic system as a known membrane-linked protein in endothelial cells, which has a role in cell migration, angiogenesis, fibrinolysis and cell proliferation. uPAR is involved in signal transduction and inducing chemotaxis in many molecules in various types of cell including endothelial cells, macrophages, lymphocytes and neutrophils (8). After cleavage from the cell surface, soluble uPAR (suPAR) levels can be determined in the blood and correlated with inflammatory markers, various cytokines and also with endothelial dysfunction, thereby showing promise as a

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biomarker for chronic inflammatory conditions. suPAR has been mentioned as a new biomarker that has outperformed CRP in determining prognosis in cardiovascular disease (9). suPAR is especially strongly expressed in endothelial cells and the formation of extracellular tissue. It has a role in extracellular matrix remodeling and angiogenesis. It has been reported that levels of suPAR are very low in healthy individuals (10). suPAR levels are elevated as a response to inflammatory conditions (11). It has also been suggested that increased suPAR levels are associated with inflammation, infection, and certain diseases including renal diseases, cardiovascular disease and cancer (12,13).

Procalcitonin is a peptide precursor of calcitonin and synthesized in the thyroid tissue and cells of the monocyte-macrophage system. High levels of procalcitonin are associated with bacterial infection. Release of procalcitonin into the bloodstream is induced by lipopolysaccharide in bacteria, detectable after 4 h. In contrast, the level of C-reactive protein (CRP) increases after 12 or 18 h in the event of bacterial inflammation. One study showed that large amounts of procalcitonin were produced after stimulation of TNF-α, interleukin-2 and interleukin-6 (14,15). The evidence indicates that serum procalcitonin level is a sensitive biomarker of bacterial infection. Serum levels of procalcitonin may be useful in diagnosing migraine diseases.

In this study, we aim to compare plasma suPAR levels in patients with migraine with/without attack to those in healthy individuals. In addition, we evaluate the usefulness of suPAR as an activity biomarker for migraine and establish a relationship between disease characteristics and levels of procalcitonin, fibrinogen and hs-CRP.

Materials and methods

Our prospective study included 60 migraine patients (45 females and 15 males; mean age 34.8 ± 9.6 years) and 30 healthy age- and gender-matched individuals (20 females and 10 males; mean age 38.2 ± 13.8 years). It was conducted in the outpatient clinic at Mugla Sıtkı Kocman University, Faculty of Medicine, Department of Neurology, according to exclusion and inclusion criteria. Migraine diagnosis criteria were recorded, based on the International Classification of Headache Disorders 2nd Edition (ICHD-II) (6). Brain MRIs were performed on all migraine patients. Exclusion criteria for migraine patients and healthy individuals were as follows: under 18 years old and over 65 years old; body mass index (BMI) $> 30\,kg/m^2$ and $< 18\,kg/m^2$; pregnancy; intake of systemic drugs such as anti-inflammatories, anticoagulants and antiaggregants; presenting of chronic disorders such as renal disease, hepatic disease and malignancy. Detailed anamneses were taken from the migraine patients, and neurological and radiological examinations were performed by the same neurologist. Eight patients whose brain MRIs revealed lacunar infarcts and 20 patients who had taken drugs were excluded from the study. This study was approved by the ethics committee of Mugla Sıtkı Kocman University's Faculty of Medicine and conducted in accordance with Declaration of Helsinki principles. Migraine attack duration, monthly frequency, aura presentation and duration of disease were recorded. The study included migraine patients in the attack period ($n = 27$); migraine patients in the interictal period ($n = 33$); migraine with aura patients ($n = 30$) and migraine without aura patients ($n = 30$). Participants' height and weight were recorded and their BMIs calculated according to World Health Organization recommendations, and expressed in kg/m^2.

Venous blood samples were taken from admitted migraine patients during the interictal and attack periods and centrifuged at $4000 \times g$ for 5 min. Serum and plasma were separated into Eppendorf tubes for analysis. Specimens were kept at −80 °C in a deep freezer until suPAR (BioVendor Laboratory Medicine Inc., Brno, Czech Republic), procalcitonin (EIA-5291, DRG International Inc., USA) and hs-CRP (BioVendor Laboratory Medicine Inc., Brno, Czech Republic) levels could be assessed using enzyme-linked immunosorbent assay (ELISA). Venous blood samples were centrifuged for 15 min at $1000 \times g$ at 4 °C within 30 min of the samples being taken. Plasma was removed and stored at −80 °C in a deep freezer until fibrinogen levels could be assayed using ELISA (Elabscience, catalog no: E-EL-H2193).

Statistical analysis

Statistical analyses were performed using SPSS 20.00 software (Chicago, IL) for Windows. All data were expressed as mean ± standard deviation. The variables were assessed using the Kolmogorov–Smirnov test for the normality of distribution. The normally distributed variables were determined using the Student's *t*-test and Pearson correlation. The other variables were calculated statistically using the Mann–Whitney *U*-test. Values of $p < .05$ were considered statistically significant.

Results

The demographic characteristics of the migraine patients and healthy individuals (control group) are shown in Table 1. No statistically significant differences in age, gender, BMI or blood pressure were found between the migraine patients and healthy individuals. Levels of suPAR and procalcitonin were found to be significantly higher in migraine patients in the attack period than in migraine patients in the interictal period and in healthy individuals ($p < .01$ for both) (Table 2, Figure 1). In the attack period, suPAR levels were higher in migraine with aura patients than in migraine without aura patients (Table 3, Figure 2). Plasma fibrinogen levels were significantly higher in migraine patients than in healthy individuals ($p < .01$). No significant differences in levels of

Table 1. Participant characteristics.

Variables	Migraine patients ($n = 60$)	Control ($n = 30$)	*p* Value
Age (years)	34.84 ± 9.68	38.2 ± 13.8	N.S
Gender (female/male)	45/15	20/10	N.S
BMI (kg/m^2)	25.37 ± 4.77	23.78 ± 5.63	N.S
Systolic BP (mmHg)	122.8 ± 14.02	120.2 ± 8.45	N.S
Diastolic BP (mmHg)	77.3 ± 8.2	79.14 ± 9.41	N.S
Hypertension (%)	12	10	N.S
Diabetes mellitus (%)	8	5	N.S

BMI: body mass index; BP: blood pressure.N.S: nonsignificant.

hs-CRP were seen between patients with migraine and the control group ($p < .05$). No significant differences in procalcitonin, hs-CRP, or fibrinogen levels were seen between the migraine with/without aura groups. When we subdivided migraine patients according to frequency of attack (attacks/month), suPAR levels in the attack period were significantly higher in the group reporting frequent attacks (4–5 or more) than in the group reporting less frequent attacks (less than 4) (Figure 3). Pearson correlation analysis of the groups revealed that variables including fibrinogen and procalcitonin were correlated with suPAR ($p = .014$, $r = -.262$; $p = .016$, $r = .225$, respectively). In addition, systolic blood pressure was found to be correlated with gender, smoking and the level of fibrinogen ($p = .01$, $r = .352$; $p = .009$, $r = -.360$; $p = .036$, $r = -.262$, respectively).

Discussion

To the best our knowledge, our study is the first to determine levels of suPAR in migraine patients. We found that the level of suPAR was elevated in migraine patients in the attack period compared to patients with migraine in the interictal period and healthy individuals. In addition, levels of suPAR were higher in migraine with aura patients than in migraine without aura patients. We suggest that suPAR might be a strong prognostic marker for migraine patients, particularly during attack periods. It may suggested that there will be possible treatments or ways in which suPAR levels could be altered pharmacologically to see whether migraine prognosis or severity of attack is affected. In previous studies, suPAR has been demonstrated to be an important and valuable

Table 2. suPAR, fibrinogen, procalcitonin, hsCRP levels in migraine in attack and interictal period and control group.

Parameters	Patients in attack ($n = 33$)	Patients in interictal period ($n = 27$)	Control	p
suPAR (pg/mL)	2361.18 ± 398.62[a]	1918.44 ± 672.87	1727.43 ± 411.4	.004
Procalcitonin (pg/mL)	320.68 ± 183.94[a]	173.21 ± 152.8	121.27 ± 57.25	.001
Fibrinogen (ng/mL)	553.61 ± 245.61	497.01 ± 235.11[b]	241.6 ± 117.9	.001
hsCRP (mg/L)	2.32 ± 2.45	2.68 ± 1.95	2.45 ± 1.98	N.S

[a]attack group versus interictal and control group.
[b]interictal group versus control group.

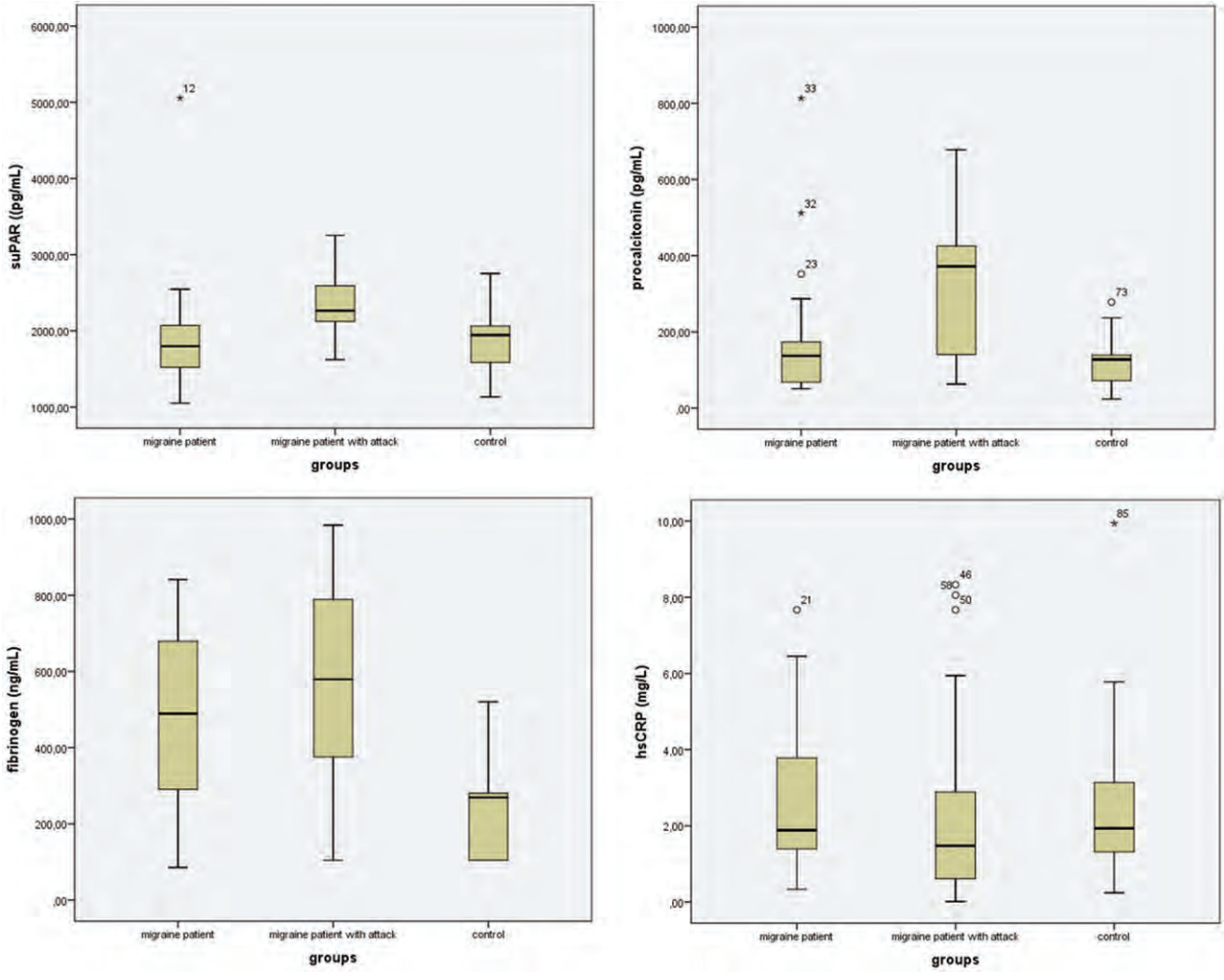

Figure 1. Serum suPAR, procalcitonin, hs-CRP and plasma fibrinogen levels in patients with migraine and control group.

biomarker in the identification of inflammatory response. The presenting of inflammation is associated to higher plasma suPAR levels. Elevated suPAR has been identified as a predictor of immune system activation and ongoing inflammatory conditions such as malignancy, ankylosing spondylitis, systemic lupus erythematosus, Behcet's disease, glomerulonephritis and cardiovascular disease (16–19). Interestingly, this contrasts with a study in which no statistically significant differences were found between the level of suPAR in patients with psoriasis who have systemic inflammation, and the level in healthy individuals. The high stability of suPAR in blood makes it a potential marker. In previous studies, higher levels of suPAR have been mentioned as predictive of severity and mortality for certain diseases including bacterial meningitis, active tuberculosis and sepsis. More importantly, suPAR levels were determined to be strong predictors of case fatality rate and allowed more accurate risk stratification than other known inflammatory markers such as CRP, procalcitonin and interleukin-6 (IL-6) (20,21). We suggest that enhanced circulating suPAR allows activative inflammation and initiates migraine attack periods. Other studies have shown that proinflammatory cytokines and chemokines are secreted during migraine attacks (22). suPAR is an acknowledged biomarker of acute and systemic inflammatory conditions. suPAR levels have been correlated with those of some proinflammatory cytokines expressed by activated monocytes, lymphocytes and neutrophils (23). suPAR is also thought to be a novel marker for activation of the inflammatory and immune systems. It is a circulating protein expressed from the cell surface of neutrophils, T cells and macrophages (24). Elevated suPAR levels may be the result of oxidative stress, endothelial cell activation and inflammation of the blood vessels from the perivascular trigeminal regions during acute attacks, as well as involved in the development of migraine attacks. On the other hand, we found high levels of suPAR in migraine with aura patients. The complex etiology of migraine with aura is still not well understood. Several studies show that migraine with aura may have an association with coagulation diseases, endothelial dysfunction and inflammation (25,26). We suggest that a complex relationship between migrainous aura and suPAR may play a role in pathophysiology, but certainly there are several other factors that may contribute to its development. Meta-analyses have demonstrated a relationship between migraine and the development of strokes. In particular, there were a rodulent association between stroke and migraine with aura in women under 45 years of age. Migraine with aura patients are more prone to thrombosis events. Our study supports these findings, showing high suPAR levels in migraine with aura patients.

Table 3. suPAR, fibrinogen, procalcitonin, hsCRP levels in migraine patients with aura and without aura subgroups.

	Migraine patients with aura ($n = 30$)	Migraine patients withou aura ($n = 30$)	p
suPAR (pg/mL)	2424.03 ± 602.59	1793.15 ± 421.92	.001
Procalcitonin (pg/mL	259.5 ± 181.6	219.59 ± 182.86	N.S
Fibrinogen (ng/mL)	492.55 ± 242.13	552.41 ± 237.15	N.S
hsCRP (mg/L)	2.51 ± 2.46	2,52 ± 1.90	N.S

N.S: nonsignificant.

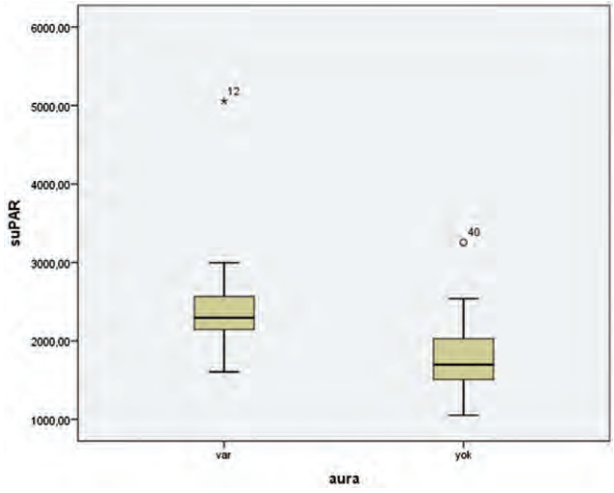

Figure 2. Serum suPAR level in migraine patients with aura and without aura.

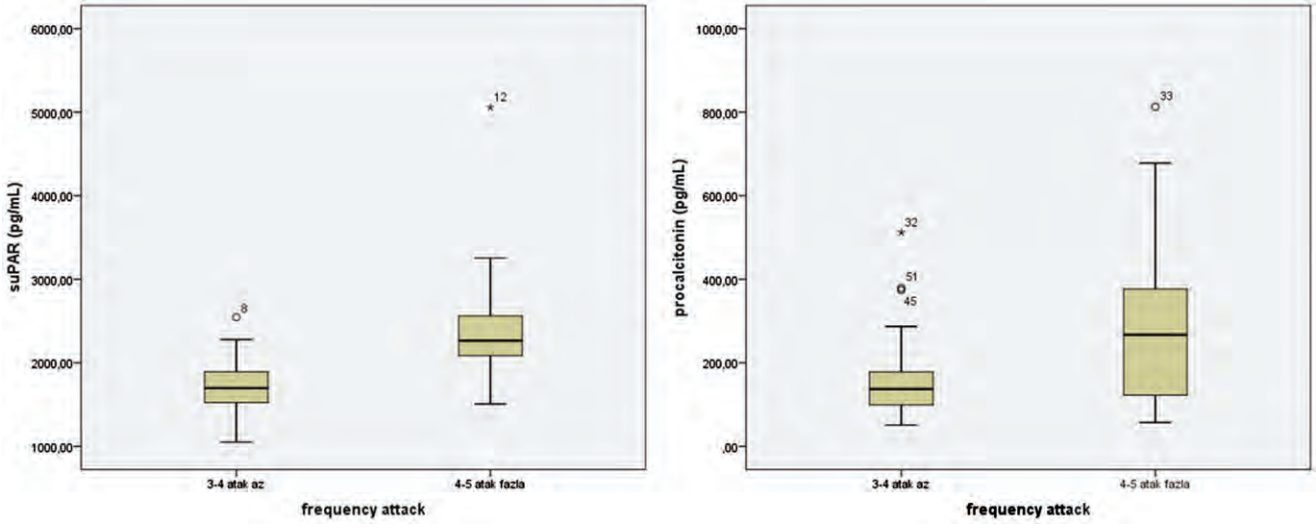

Figure 3. Serum suPAR and procalcitonin levels in frequency of attack (attacks/month) in patients with migraine.

Regarding the above-mentioned reports of an association between increased procalcitonin levels and several inflammatory disorders, our study found statistically significant differences between the serum procalcitonin levels of migraine patients and those of healthy individuals. Similarly, Turan et al. found increased levels of procalcitonin in migraine patients during the attack period compared to migraine patients during the periods between attacks (27). In addition, they suggested that serum procalcitonin levels in migraine without aura patients during the attack period were higher than in patients during the periods in between attacks. On the contrary, our findings showed strong evidence of a relationship between procalcitonin levels and migraine attack.

Fibrinogen is well known as a major coagulation protein and also as an inflammatory marker. It is clear that fibrinogen is a crucial protein for determining risk of vascular events, as it has a role in blood viscosity and platelet aggregation. It has been documented that migraine is related to endothelial dysfunction and that dysfunction correlates with the severity of the disease (28). Endothelial injury results in elevation of fibrinogen levels; elevated plasma fibrinogen contributes to the endothelial dysfunction and eventually leads to migraine. The vascular inflammation may reflect the endothelial dysfunction and activation of the coagulation factors. Chronic migraine is known to be associated with thrombotic events (29). Two prospective studies found an association between high plasma fibrinogen and increased risk of migraine, although there were some differences in the two studies' results. In the first of these, Yucel et al. determined that migraine patients have increased plasma fibrinogen compared to healthy individuals. They found no differences in the fibrinogen levels in migraine patients in the attack and interictal periods (30). This is similar to our study, which found no statistically significant differences between plasma fibrinogen levels in patients with migraine during attack and those in the interictal period. The second of these prospective studies found no differences in the levels of fibrinogen and CRP in patients with migraine compared to healthy individuals (31). However, no previous study examines the relationship between levels of plasma fibrinogen along with those of suPAR, hs-CRP, and procalcitonin. We found a positive correlation between levels of fibrinogen, suPAR and procalcitonin.

Previous studies have reported an association between cardiovascular diseases, atherosclerosis and migraine (32,33). Today, it is known that hs-CRP and IL-6 levels are related to higher risk of cardiovascular disorders. We found no difference in levels of hs-CRP in migraine patients compared to healthy individuals. Interestingly, our data points to superiority of suPAR compared to hs-CRP. Consistent with the present findings, Reichsoellner et al. reported suPAR's superiority for prognosis over various inflammatory markers such as CRP, IL-8, IL-10 and neutrophil gelatinase-associated lipocalin (NGAL) (34). Various studies mention high levels of hs-CRP in migraine without aura patients (22,35–37). In one previous study, the presence of aura was associated with ischemic stroke (38). So that, this reports is not correlated to previous studies. Nermin et al. report elevated hs-CRP levels in migraine patients (32). In contrast, other reports have found that hs-CRP levels were not elevated in migraine patients compared to healthy individuals (39–41). These differences may be related to differences in the mean age of participiants. In the current study, we included younger participants compared to previous studies. hs-CRP is known to be associated with vascular risk factors. We also included more female migraine patients in our study because the frequency of migraine headaches is nearly three times greater in women than in the male population (42). The heavier proportions of younger and female participants in our study may be the reason for our finding no significant difference in the levels of hs-CRP in migraine patients versus healthy individuals. In another study, it was reported that levels of fibrinogen and CRP were higher in migraine patients than in healthy individuals. The same study found no significant difference in levels of fibrinogen and CRP in patients with episodic migraine compared to those with chronic migraine (43). Clinical studies have shown that drug therapies, especially those using anti-inflammatory agents, are effective for migraine patients (44). The inflammatory hypothesis was validated in several studies, which found a relationship between two inflammatory markers, CRP and pentraxine 3 and migraine disease (6). However, the current findings point to a stronger suPAR-migraine association than exists between hs-CRP and migraine. We did not observe anything that differs significantly from previous studies in terms of the relationship between hs-CRP and migraine. It may support inflammatory processes, and other pathways may play a role in the presenting of migraine attacks and aura.

The number of studies investigating the level of suPAR on various infectious and inflammatory diseases. It would be interesting to evaluate the usefulness of systemic levels of suPAR in serum for determining on treatment. suPAR seems a promising prognostic marker in migraine patients. There are confusing that which treatment effective on the migraine disease characterize. Future studies should show whether prognostic assessment translates into better clinical outcomes.

Conclusions

To the best of our knowledge, this study is the first to conclude that suPAR level may be considered a new risk factor for migraine attack and aura presentation. The finding is based on the reported elevated levels of suPAR, procalcitonin and fibrinogen in patients with migraine, which support the hypothesis that occurring sterile inflammation may play a role in migraine pathogenesis.

Disclosure statement

No potential conflict of interest was reported by the author.

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References

1. Ertas M, Baykan B, Orhan EK, et al. One-year prevalence and the impact of migraine and tension-type headache in Turkey: a nationwide home-based study in adults. J Headache Pain 2012;13:147–57.
2. Bolay H, Reuter U, Dunn AK, et al. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med 2002;8:136–42.
3. Waeber C, Moskowitz MA. Migraine as an inflammatory disorder. Neurology 2005;2464:S9–S15.
4. Olesen J. International Classification of Headache Disorders, Second Edition (ICHD-2): current status and future revisions. Cephalalgia 2006;26:1409–10.
5. Avci AY, Lakadamyali H, Arikan S, et al. High sensitivity C-reactive protein and cerebral white matter hyperintensities on magnetic resonance imaging in migraine patients. J Headache Pain 2015;16:9.
6. Ceylan M, Bayraktutan OF, Becel S, et al. Serum levels of pentraxin-3 and other inflammatory biomarkers in migraine: association with migrainecharacteristics. Cephalalgia 2016;36:518–25.
7. Enocsson H, Wetterö J, Skogh T, Sjöwall C. Soluble urokinase plasminogen activator receptor levels reflect organ damage in systemic lupus erythematosus. Transl Res 2013;162:287–96.
8. Smith HW, Marshall CJ. Regulation of cell signalling by uPAR. Nat Rev Mol Cell Biol 2010;11:23–36.
9. Arbel Y, Strauss BH. suPAR: a cardiac biomarker with a future? Can J Cardiol 2015;31:1223–4.
10. Stephens RW, Pedersen AN, Nielsen HJ, et al. ELISA determination of soluble urokinase receptor in blood from healthy donors and cancer patients. Clin Chem 1997;43:1868–76.
11. Ostrowski SR, Piironen T, Høyer-Hansen G, et al. High plasma levels of intact and cleaved soluble urokinase receptor reflect immune activation and are independent predictors of mortality in HIV-1-infected patients. J Acquir Immune Defic Syndr 2005;39:23–31.
12. Huttunen R, Syrjanen J, Vuento R, et al. Plasma level of soluble urokinase-type plasminogen activator receptor as a predictor of disease severity and case fatality in patients with bacteraemia: a prospective cohort study. J Intern Med 2011;270:32–40.
13. Langkilde A, Hansen TW, Ladelund S, et al. Increased plasma soluble uPAR level is a risk marker of respiratory cancer in initially cancer-free individuals. Cancer Epidemiol Biomarkers Prev 2011;20:609–18.
14. Lee JY, Hwang SJ, Shim JW, et al. Clinical significance of serum procalcitonin in patients with community-acquired lobar pneumonia. Korean J Lab Med 2010;30:406–13.
15. Pourakbari B, Mamishi S, Zafari J, et al. Evaluation of procalcitonin and neopterin level in serum of patients with acute bacterial infection. Braz J Infect Dis 2010;14:252–5.
16. Soltysiak J, Zachwieja J, Benedyk A, et al. Circulating suPAR as a biomarker of disease severity in children with proteinuric glomerulonephritis. Minerva Pediatr 2016. [Epub ahead of print].
17. Kurtipek GS, Kesli R, Akyurek FT, et al. Plasma-soluble urokinase plasminogen activator receptor (suPAR) levels in Behçet's disease and correlation with disease activity. Int J Rheum Dis 2016. [Epub ahead of print]. doi: 10.1111/1756-185X.12873.
18. Kurtipek GS, Kesli R, Akyürek FT, et al. Plasma-soluble urokinase plasminogen activator receptor (suPAR) levels in psoriasis patients and correlation with disease severity. Acta Dermatovenerol Alp Pannonica Adriat 2015;24:73–5.
19. Cyrille NB, Villablanca PA, Ramakrishna H. Soluble urokinase plasminogen activation receptor – an emerging new biomarker of cardiovascular disease and critical illness. Ann Card Anaesth 2016;19:214–16.
20. Uusitalo-Seppälä R, Huttunen R, Tarkka M, et al. Soluble urokinase-type plasminogen activator receptor in patients with suspected infection in the emergency room: a prospective cohort study. J Intern Med 2012;272:247–56.
21. Koch A, Tacke F. Risk stratification and triage in the emergency department: has this become 'suPAR' easy? J Intern Med 2012;272:243–6.
22. Bockowski L, Sobaniec W, Zelazowska-Rutkowska B. Proinflammatory plasma cytokines in children with migraine. Pediatr Neurol 2009;41:17–21.
23. Edsfeldt A, Nitulescu M, Grufman H, et al. Soluble urokinase plasminogen activator receptor is associated with inflammation in the vulnerable human atherosclerotic plaque. Stroke 2012;43:3305–12.
24. Borné Y, Persson M, Melander O, et al. Increased plasma level of soluble urokinase plasminogen activator receptor is associated with incidence of heart failure but not atrial fibrillation. Eur J Heart Fail 2014;16:377–83.
25. Dalkara T, Nozari A, Moskowitz MA. Migraine aura pathophysiology: the role of blood vessels and microembolisation. Lancet Neurol 2010;9:309–17.
26. Murinova N, Krashin DL, Lucas S. Vascular risk in migraineurs: interaction of endothelial and cortical excitability factors. Headache 2014;54:583–90.
27. Turan H, Horasanli B, Ugur M, Arslan H. Procalcitonin levels in migraine patients. Can J Neurol Sci 2011;38:124–8.
28. Fibrinogen Studies Collaboration, Kaptoge S, White IR, Thompson SG, et al. Associations of plasma fibrinogen levels with established cardiovascular disease risk factors, inflammatory markers, and other characteristics: individual participant meta-analysis of 154,211 adults in 31 prospective studies: the fibrinogen studies collaboration. Am J Epidemiol 2007;166:867–79.
29. Nielsen VG, Kulin W, LaWall JS, et al. Chronic migraineurs form carboxyhemefibrinogen and iron-bound fibrinogen. CNS Neurol Disord Drug Targets 2015;14:1079–85.
30. Yucel Y, Tanriverdi H, Arıkanoglu A, et al. Increased fibrinogen, D-dimer and galectin-3 levels in patients with migraine. Neurol Sci 2014;35:545–9.
31. Yilmaz N, Aydin O, Yegin A, et al. Increased levels of total oxidant status and decreased activity of arylesterase in migraineurs. Clin Biochem 2011;44:832–7.
32. Wabnitz A, Bushnell C. Migraine, cardiovascular disease, and stroke during pregnancy: systematic review of the literature. Cephalalgia 2015;35:132–9.
33. Li H, Yu Y. Association between ischemic stroke and migraine in elderly Chinese: a case-control study. BMC Geriatr 2013;13:126.
34. Reichsoellner M, Raggam RB, Wagner J, et al. Clinical evaluation of multiple inflammation biomarkers for diagnosis and prognosis for patients with systemic inflammatory response syndrome. J Clin Microbiol 2014; 52:4063–6.
35. Kurth T, Tzourio C, Bousser MG. Migraine: a matter of the heart? Circulation 2008;118:1405–7.
36. Vanmolkot FH, de Hoon JN. Increased C-reactive protein in young adult patients with migraine. Cephalalgia 2007;27:843–6.
37. Güzel I, Tas demir N, Celik Y. Evaluation of serum transforming growth factor b1 and C-reactive protein levels in migraine patients. Neurol Neurochir Pol 2013;47:357–62.
38. Kurth T, Schürks M, Logroscino G, et al. Migraine, vascular risk, and cardiovascular events in women: prospective cohort study. BMJ 2008;337:a636.
39. Gudmundsson LS, Aspelund T, Scher AI, et al. C-reactive protein in migraine sufferers similar to that of non-migraineurs: the Reykjavik Study. Cephalalgia 2009;29:1301–10.
40. Guldiken B, Guldiken S, Demir M, et al. Insulin resistance and high sensitivity C-reactive protein in migraine. Can J Neurol Sci 2008;35:448–51.
41. Guldiken S, Guldiken B, Demir M, et al. Soluble CD40 ligand and prolactin levels in migraine patients during interictal period. J Headache Pain 2011;12:355–60.
42. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004;24:9–160.
43. Van Dongen RM, Zielman R, Noga M, et al. Migraine biomarkers in cerebrospinal fluid: a systematic review and meta-analysis. Cephalalgia 2017;37:49–63.
44. Lippi G, Mattiuzzi C, Cervellin G. C-reactive protein and migraine. Facts or speculations? Clin Chem Lab Med 2014;52:1265–72.