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ORIGINAL ARTICLE

Association of serum levels of intercellular adhesion molecule-1 and interleukin-6 with migraine

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Abstract To investigate the associations of serum levels of intercellular adhesion molecule-1 (ICAM1) and the pro-inflammatory cytokine interleukin-6 (IL-6) with migraine and migraine subtypes, and to study their correlation with each other in this condition. We used enzyme-linked immunosorbent assay to measure serum levels of ICAM1 and IL-6 in 103 migraine patients with and without aura, in both attack and pain-free periods, and in 100 healthy control subjects. Serum levels of ICAM1 and IL-6 were significantly higher in migraine patients during attacks than in controls ($p < 0.05$). Serum ICAM1 levels were significantly higher in migraine with aura (MA) than in migraine without aura (MO), ($p < 0.05$). Correlation analysis indicated a significant positive correlation between serum levels of ICAM1 and IL-6 ($p < 0.05$) in migraine patients during attacks. Our results indicate that ICAM1 and IL-6 are involved in the pathogenesis of migraine attacks, possibly via an interactive mechanism.

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Introduction

Although migraine is a common neurological disease, its pathogenesis remains unclear. The prevalent trigeminal neurovascular reflex theory of migraine attributes this condition to a combination of neurogenic inflammation induced by vasoactive peptides released by perivascular nerves, dilation of intracranial and extracranial vessels and decreased inhibition of central pain transmission [1]. Specifically, during migraine attacks, stimulation of trigeminal nerve fibers in the dura mater triggers the release of calcitonin gene-related peptide (CGRP) and other vasoactive substances, leading to neurogenic inflammation of the dura and peripheral tissues [2–4].

Neurogenic inflammation arising from the trigeminal neurovascular reflex has been linked with intercellular adhesion molecule-1 (ICAM1/CD54) and inflammatory cytokines including TNFA and interleukins -2 (IL-2), -10 (IL-10) and -6 (IL-6) [5–9]. IL-6 is widely produced in the initial phase of acute and chronic inflammation by fibroblasts, endothelial cells, macrophages, lymphocytes and neutrophils. It has been reported to play a significant role in the regulation of pain threshold and trigeminal nerve fiber sensitization in migraine [10] and is thought to facilitate pain signaling from the meninges during the development of headache [11]. ICAM1 is an adhesion molecule of the immunoglobulin superfamily that regulates the infiltration of leukocytes in inflammatory tissue. ICAM1 is distributed primarily on the surface of lymphocytes, neutrophils, epithelial cells, mononuclear macrophage and vascular endothelial cells [12], and its

expression is reportedly regulated by interleukin-1β (IL-1β), TNF-α, IFN-γ and LPS [13].

The relationship between serum levels of ICAM1 and migraine is the subject of controversy. Although transient elevation of serum ICAM1 has been reported in migraine or pain stress [5, 6], another study has documented a decrease in these levels in migraine patients [7]. Interestingly, although IL-6 has been shown to promote ICAM1 expression in polymyositis [14], correlations between serum IL-6 and ICAM1 levels in migraine during attacks have to date not been reported. Here, in an effort to shed light on their role in this condition, we measured and correlated serum levels of ICAM1 and IL-6 in migraine and migraine subtypes.

Materials and methods

Subjects

Source and grouping

The migraine group consisted of 103 individuals (61 females and 42 males, mean age = 25.02 ± 8.69 years) consecutively diagnosed with migraine at the People's Hospital of Liaoning Province between March 2011 to December 2013, of which 72 were migraine without aura (MO) and 31 were migraine with aura (MA). Initial attacks in this group occurred mostly in the 10–30 years age range (78.64 %), with relatively few (21.36 %) occurring in the 31–48 years age range. 68 of patients were non-manual workers and 35 were manual workers. The control group consisted of 100 age- and gender-matched volunteers and workers (59 women and 41 men, mean age = 24.24 ± 8.48 years) at the People's Hospital of Liaoning Province, selected over the same period, and who had no personal or family history of migraine. Of the controls, 68 were non-manual workers and 32 were manual workers. All subjects gave informed consent for participation in this study. The study was reviewed and approved by our department board.

Inclusion and exclusion criteria

All subjects underwent detailed neurological examination, took a researchers' questionnaire survey, and underwent tests for transcranial doppler sonography (TCD), head computed tomograph (CT), head magnetic resonance angiography (MRA), electrocardiogram (ECG), white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood sugar and lipids. Patients were diagnosed by two neurologists, according to the 2004 Headache Classification Committee of International Headache Society (IHS) migraine diagnosis standard [15]. All patients in the migraine group had not received any prophylactic migraine medication in the previous week, and had not taken antibiotics within the previous 3 months. Patients who had non-migraine headache, inflammatory or autoimmune diseases, abnormal CRP levels, hypertension, diabetes mellitus, obesity, metabolic syndrome or ischemic cerebrovascular disease were excluded from this study.

Methods

Blood sample collection

2 mL of peripheral venous blood samples was obtained during headache-free intervals, at least 3 days since the previous attack and at 2 h after attack onset. Immediately after drawing, blood was mixed with EDTA anticoagulant, centrifuged at 1,000 rpm for 15 min and stored at −20 °C. After blood sampling during attack, patients were given symptomatic medication.

Determination of serum ICAM1 and IL-6 levels

Human ICAM1 and IL-6 enzyme-linked immunosorbent assay (ELISA) kits No. EK0370 and No. EK0410 (Wuhan Boster Biological Engineering Company, Beijing, China) were used to measure serum ICAM1 and IL-6 levels in accordance with the manufacturer's instructions.

Statistical analysis

All statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Since data showed normal distribution, *t* test for independent samples was conducted for comparison between patients and controls, MA and MO, and *t* test for dependent samples was conducted for comparison between measurements during attack and attack-free periods within the patients' group. Correlation test was analyzed by Pearson correlation, with bilateral $p < 0.05$ taken to represent statistical significance.

Results

General clinical data

No differences were found between the migraine and the control groups with respect to age, gender and occupation ($p > 0.05$, Table 1). Of the 103 migraine patients, 54 had a family history. Aura symptoms were visual abnormalities, including 17 cases of flash, 6 cases of blurred vision, 5 cases of dark spots and 3 cases of visual field defect. The number of migraines with throbbing headache, tightness,

and uncertain headache was 69, 28 and 6 respectively. With respect to location, headaches were reported in the temple (64), forehead or orbit (21), parietal lobe (11) and uncertain site (7).

Serum levels of ICAM1

Serum levels of ICAM1 in the migraine patients and the control group are shown in Table 2. Compared with those in healthy controls (1,770.1 ± 268.2) pg/ml, serum ICAM1 levels were higher 2 h after attack onset in all migraine patients (2,689.6 ± 584.9) pg/ml, as well as the MA (3248.8 ± 494.5) pg/ml and MO (2448.4 ± 439.0) pg/ml subgroups (all $p < 0.05$), but not in the pain-free period. In addition, serum ICAM1 levels in MA during attack were significantly higher than those in MO during attack ($p < 0.05$).

Table 1 Comparison of age, gender and occupation between the migraine and control groups

	Migraine group	Control group	*p*
Age	25.02 ± 8.69	24.24 ± 8.48	0.519
13–20 years	44 (42.72 %)	45 (45.00 %)	
21–30 years	37 (35.92 %)	35 (35.00 %)	
31–48 years	22 (21.36 %)	20 (20.00 %)	
Sex			0.974
Male	40.78 %	41.00 %	
Female	59.22 %	59.00 %	
Occupation			0.764
Mental workers	66.02 %	68.00 %	
Manual workers	33.98 %	32.00 %	

Table 2 Serum levels of ICAM1 in the migraine and control groups

Group	*n*	ICAM1 (mean ± SD, pg/ml)
(A) Migraine (attack period)	103	2689.6 ± 584.9[a,e]
(A1) MA	31	3248.8 ± 494.5[a,c,e]
(A2) MO	72	2448.9 ± 439.0[a,e]
(B) Migraine (pain-free period)	103	1781.4 ± 317.9[b]
(B1) MA	31	1795.2 ± 324.1[b,d]
(B2) MO	72	1775.4 ± 317.3[b]
(C) Control	100	1770.1 ± 268.2

Group A: migraine (attack period), group B: migraine (pain-free period), group C: control group; A1: migraine with aura during attack period, A2: migraine without aura during attack period; B1: migraine with aura during pain-free period, B2: migraine without aura during pain-free period

[a] Significant difference between the migraine group (group A, A1, A2) and the control group (group C) ($t = 14.5, 15.9, 11.6$; $p < 0.001$, $p<0.001$, $p < 0.001$, respectively)

[b] No difference in serum ICAM1 levels between the migraine group (group B, B1, B2) and the control group (group C) ($t = 0.27, 0.433, 0.118$; $p = 0.786, 0.665, 0.906$, respectively)

[c] Significant difference in serum ICAM1 levels between the A1 and A2 groups ($t = 8.2$, $p < 0.001$)

[d] No difference in serum ICAM1 levels between the B1and B2 group ($t = 0.289$, $p = 0.773$)

[e] Significant difference in serum ICAM1 levels between migraine during attack period (group A, A1, A2) and pain-free period (group B, B1, B2) ($t = 23.7, 12.9, 23.5$; $p < 0.001$, $p < 0.001$, $p < 0.001$, respectively)

Serum levels of IL-6

Compared with healthy controls (23.14 ± 10.64) pg/ml, serum levels of IL-6 were significantly higher in the attack and pain-free periods of migraine (54.57 ± 22.01 and 53.36 ± 22.59, respectively), MA (59.80 ± 22.07 and 57.22 ± 24.50, respectively) and of MO (52.31 ± 21.75 and 51.69 ± 21.69, respectively) patients (all $p < 0.05$) (Table 3).

Correlation analysis of ICAM1and IL-6

Pearson correlation analysis indicated a positive correlation between serum ICAM1 and IL-6 levels in migraine patients during attacks ($r = 0.734$, $p < 0.001$) (Fig. 1), in the MA subtype ($r = 0.893$, $p < 0.001$) and in the MO subtype ($r = 0.825$, $p < 0.001$). In migraine patients during the

Table 3 Serum levels of IL-6 between the migraine group and the control group

Group	*n*	IL-6 (mean ± SD, pg/ml)
(A) Migraine (attack period)	103	54.57 ± 22.01[a,e]
(A1) MA	31	59.80 ± 22.07[a,c,e]
(A2) MO	72	52.31 ± 21.75[a,e]
(B) Migraine (pain-free period)	103	53.36 ± 22.59[b]
(B1) MA	31	57.22 ± 24.50[b,d]
(B2) MO	72	51.69 ± 21.69[b]
(C) Control	100	23.14 ± 10.64

Group A: migraine (attack period) group B: migraine (pain-free period) group C: control group; A1: migraine with aura during attack period A2 migraine without aura during attack period; B1: migraine with aura during pain-free period B2: migraine without aura during pain-free period

[a] Significant difference in serum IL-6 levels between the migraine group (group A, A1, A2) and the control group (group C) ($t = 13.01, 8.93, 10.51$; $p < 0.001$, $p < 0.001$, $p < 0.001$, respectively)

[b] Significant difference in serum IL-6 levels between the migraine group (group B, B1, B2) and the control group (group C) ($t = 12.25, 7.53, 10.31$; $p < 0.001$, $p < 0.001$, $p < 0.001$, respectively)

[c] No difference in serum IL-6 levels between the A1 and A2 group ($t = 1.596$, $p = 0.114$)

[d] No difference in serum IL-6 levels between the B1and B2 group ($t = 1.14$, $p = 0.257$)

[e] No difference in serum IL-6 levels between migraine during attack period (group A, A1, A2) and pain-free period (group B, B1, B2) ($t = 0.392, 0.420, 0.174$; $p = 0.696, 0.667, 0.862$, respectively)

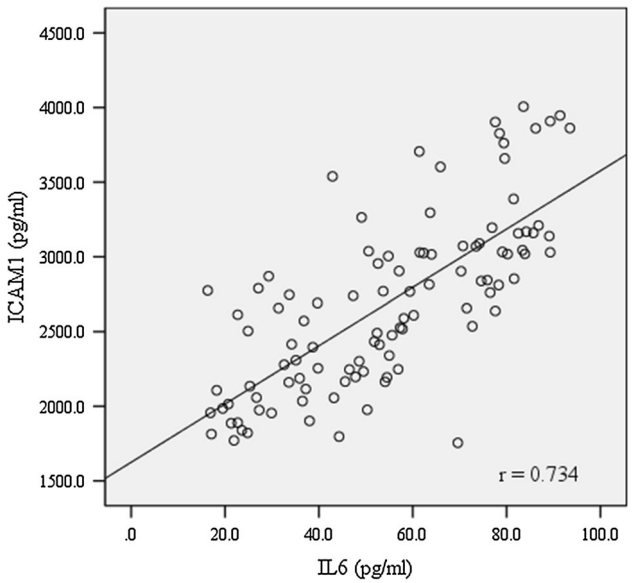

Fig. 1 Correlation analysis of serum levels of ICAM1 and IL-6 during migraine attacks

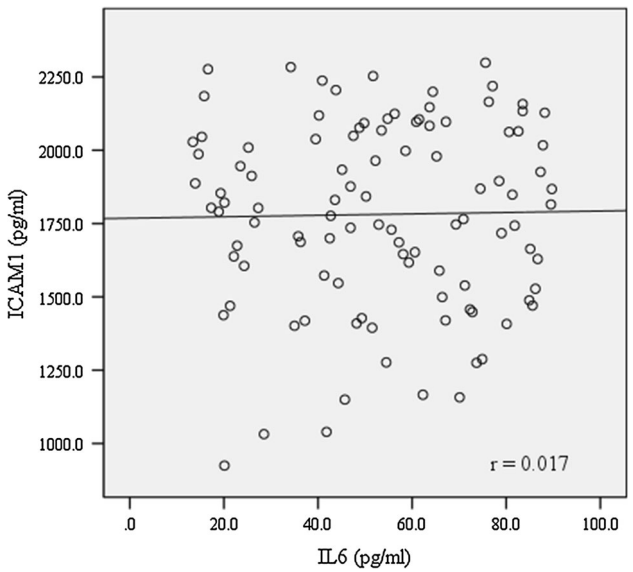

Fig. 2 Correlation analysis of serum levels of ICAM1 and IL-6 during migraine pain-free period

pain-free period, however, we found no correlation between ICAM1 and IL-6 levels ($r = 0.017$, $p = 0.862$) (Fig. 2), and subgroup analysis showed ICAM-1 and IL-6 levels did not correlate in MA ($r = -0.031$, $p = 0.870$) or MO ($r = 0.036$, $p = 0.763$).

Discussion

Abundant evidence links migraine to neurogenic inflammation induced by trigeminal nerve fibers and epidural vasodilation [8–10], and points to a role for the inflammatory mediator ICAM1 and the pro-inflammatory cytokine IL-6 in this process. High levels of pro-inflammatory cytokines are thought to stimulate the activation of trigeminal nerve, which results in the release of vasoactive peptides and other biological mediators, ultimately leading to neurogenic inflammation [16]. A specific role has been suggested for IL-6 in the modulation of pain threshold and sensitization of trigeminal nerve fibers. Here, we measured and carried out, to our knowledge for the first time, correlative analysis of serum ICAM1 and IL-6 levels in migraine patients.

Serum levels of ICAM1 in migraine patients

Although the role of ICAM1 in pain-induced neurogenic inflammation is supported by increased brainstem levels of ICAM1 in mice receiving facial carrageenan injections [17], the relationship between serum levels of ICAM1 and migraine in humans remains controversial. For example, transient increases in soluble intercellular adhesion molecule-1 (*s*ICAM1) levels have been detected in the jugular vein in the first 2 h after migraine attack onset [5], and blood levels of platelet membrane adhesion molecules are known to decrease in response to therapeutic migraine medication [18]. Moreover, in this study, we found that, compared with controls, serum levels of ICAM1 were significantly higher in migraine patients in the 2 h after attack onset, but not in the pain-free period. In contrast, however, decreased serum ICAM1 levels have been demonstrated during migraine attacks induced by administration of isosorbide dinitrate.

We speculate that discrepancies between these studies with respect to serum ICAM1 levels and migraine may be attributable to different time points at which measurements were made. In early stage of migraine onset, increased ICAM1 production by vascular endothelium of peripheral sensory nerve fibers leads to increased leukocyte infiltration in the inflammatory tissue. This in turn causes the release of endogenous opioid peptides to effect analgesia [6], while neuropeptides released from the trigeminal nerve fibers promote further production of ICAM1. In the late stage of attack and during the pain-free period, decreased ICAM1 production may inhibit the critical step of transendothelial migration of activated leukocytes into the cerebral tissues, thereby preventing sterile inflammation. Although the mechanism underlying fluctuations in ICAM1 levels in migraine during attack is unclear, one hypothesis invokes increased levels during attacks of nuclear transcription factor-κB (NF-κB) [19, 20]. Specifically, transcriptional activation of the ICAM1 gene by activated NF-κB is thought to lead to increased levels of ICAM1 protein [17] that, via interactions with LFA-1 or

Mac-1, mediate cell–cell adhesion and a subsequent meningeal inflammatory response.

We also found that serum ICAM1 levels were higher in MA than those in MO, suggesting an association between ICAM1 and visual aura. One model for migraine aura posits that activation by cortical spreading depression (CSD) of trigeminal nerve fibers in the dura promotes release of CGRP, leading to vasodilation, plasma protein extravasation and neurogenic inflammation [21]. Moreover, a genetic study has implicated genes encoding ion transporters in familial hemiplegic migraine, suggesting that disturbances in ion and neurotransmitter balances in the brain may be responsible for migraine aura [22]. Based on these findings, we speculate that the higher serum levels of ICAM1 in MA shown by our study are related to the regulation of CGRP production by neurotransmitters and ions.

Serum levels of IL-6 in migraine patients

The report of a dose-dependent reduction of IL-6 secretion by microglia pretreated with the migraine medication parthenolide (PTN) supports an indirect role for IL-6 in the inflammatory response [23]. IL-6 is thought to mediate activation of up to 20 % of meningeal nociceptors in the trigeminal ganglion in mice [24]. Its mechanism of action is thought to relate to decreasing the threshold for action potential firing in trigeminal neurons. This leads to more frequent and numerous action potentials and increased phosphorylation of the sodium channel, leading to sensitization of dural afferents and ultimately contributing to the pathogenesis of migraine [11].

We found that serum IL-6 levels were higher in migraine patients than in controls and that, consistent with a previous study [25], they did not differ between migraine patients during headache attacks and in the interictal period. The mechanism underlying the role of IL-6 and migraine is thought to involve induction of the IL-6 gene by NF-κB, Fos/jun and glucocorticoid receptor [26–28], leading to increased IL-6 signaling via the extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK) signal transduction pathways in the trigeminal ganglion neurons. This in turn results in increased pain and induction of central sensitization and hyperalgesia by increasing excitatory synaptic transmission or decreasing inhibitory synaptic transmission [11, 29]. Our finding that serum levels of IL-6 are elevated in migraine patients during both the attack and pain-free periods suggests that increased IL-6 levels may increase susceptibility to chronic migraine attacks. We infer, therefore, that persistent elevation of IL-6 levels might be one of the causes of treatment refractory chronic migraine, and suggest that decreasing IL-6 levels in migraine patients may be an attractive therapeutic option.

Correlation of ICAM1 and IL-6 in migraine attacks

Locally secreted IL-6 has been shown to regulate ICAM1 levels and promote monocyte chemotaxis and leukocyte trafficking in autoimmune polymyositis and during rejection of transplanted myoblasts [14]. Moreover, IL-6 induction of endothelial ICAM1 in trauma has been shown to result in increased neutrophil and endothelial adhesion [30]. Hypothesizing that interactions between these inflammatory mediators might contribute migraine attack, we analyzed the correlation between serum ICAM1 and IL-6 levels in migraine patients. Our data show, to our knowledge for the first time, that serum ICAM1 and IL-6 levels are positively correlated with migraine, and suggest that a synergistic relationship between ICAM1 and IL-6 during migraine attacks. The fact that positive correlation was not observed in migraine patients during the pain-free period, however, suggests that during acute migraine attacks, the activation of certain signaling pathways by inflammatory factors might support IL-6 induction of ICAM-1 activity. Binding of IL-6 with soluble gp80 (sIL-6R) has been shown to regulate monocyte chemotactic protein-1 (MCP1) and ICAM1, resulting in activation of inflammatory cells and increased monocyte chemotaxis and leukocyte trafficking [14]. Moreover, IL-6-induced ICAM1 expression and cell migration have been shown to be repressed by specific inhibitors and siRNAs targeting components of the ILK, Akt and AP-1 cascades. Taken together, these results indicate that IL-6 positive regulates ICAM1 via activation of the ILK/Akt/AP-1 pathway [31]. Our observation that IL-6 and ICAM1 levels are correlated with migraine suggests that inhibition of IL-6/ICAM1 signaling holds potential for the treatment of neurogenic inflammation.

In concert, our data suggest that increased plasma levels of IL-6 and ICAM1 might be related to pathophysiologic dysfunction during in migraine, and that these factors may have a synergistic relationship during migraine attacks. Moreover, our findings raise the possibility that the development of drugs that effect decreases in IL-6 and ICAM1 levels in migraine patients might be an attractive therapeutic option. Finally, our work implies that levels of IL-6 and ICAM1 may be related to clinical responses, and might assist in the objective evaluation of clinical response in migraine after prophylactic therapy.

Conflict of interest The authors have no conflict of interest to declare.

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