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Research Article

Is there an association between migraine and atopic disorders? The results of multicenter migraine attack study

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Summary

We designed this multicenter study to evaluate the abnormalities related to the mast cell activation during attacks in a large group of migraineurs and to compare the findings both with episodic tension type headache (ETTH) and matched healthy control subjects. After the evaluation of diagnostic criteria, 213 subjects were included in this study after giving consent. Of all 146 subjects (67.8%) were migraineurs, 38 (19.4%) were ETTH patients and 29 others were healthy controls matched according to age and sex. Immunological screening showed significantly high ratios of IL-1β, IL-2, IL-6 and TNF-α in the migraine group compared to ETTH (16.6% vs 10.5%, 20.0% vs 5.3%, 13.8% vs 2.6% and 15.9% vs 5.3%, respectively) and to the healthy controls. Logistic regression analysis showed that only duration of headache has an important effect on having IL-2 abnormality (Exp-B: 0.322, 95% CI: 0.151-0.688, p=0.003) in patients with migraine. There was no important effect of clinical variables on serological abnormalitites or each other. In conclusion, our multicenter clinical and laboratory based study suggests that primary headache disorders (migraine and ETTH) are associated with atopic changes and they might share the inflammatory mechanism (pro-inflammatory as well as anti-inflammatory cytokine abnormalities) during headache attacks.

Key words: Migraine, tension type headache, cytokine, immunologic, pro-inflammatory, anti-inflammatory.

Migre ile Atopik Bozukluklar Arasında Bir İlişki Varmıdır? Çok Merkezli Migren Atak Çalışması

Özet

Bu çok merkezli çalışmayı geniş bir grup migren hastasında ataklarda mast hücre aktivasyonuna bağlı anormallikleri değerlendirebilmek ve bulguları Epizodik Gerilim Tip Başağrısı (EGTB) ve sağlıklı kontroller ile kıyaslayabilmek amacı ile planladık. Tanı

kriterleri açısından yapılan dikkatli bir değerlendirme sonrasında çalışmaya onam veren 213 olgu alındı. Bu olguların 146'sı migren (%67.8), 38'i (%19.4)EGTB ve 29'u yaş ve cins açısından uyumlu sağlıklı kontrol idi. İmmunolojik incelemeler migrenli olgularda EGTB ve sağlıklı kontroller ile kıyaslandığında anlamlı oranlarda yüksek IL-1 beta, IL-2, IL-6 ve TNF-α oranlarını (sırasıyla 16.6% vs 10.5%, 20.0% vs 5.3%, 13.8% vs 2.6% and 15.9% vs 5.3%) gösterdi. Lojistik regresyon analizi migrenli olgularda yalnızca başağrısı süresinin IL-2 anormalliği üzerinde anlamlı etkisi (Exp-B: 0.322, %95 CI: 0.151-0.688, p=0.003) olduğunu gösterdi. Bunun dışında klinik ve immunolojik değişknelerin birbiri üzerinde anlamlı etkisi saptanmadı. Sonuç olarak çok merkezli klinik ve laboratuvar temelli migren atak çalışması bulgularımız primer başağrısı bozuklukları (migren ve EGTB) ile atopik değişiklikler arasında ilişki olduğunu ve başağrısı atakları sırasında inflamatuar mekanizmalara (pro-inflamatuar ve anti-inflamatuar tipte sitokin anormallikleri) ait ortak bulguları taşıdıklarını destekledi.

Keywords: Migren, epizodik gerilim tipi başağrısı, sitokin, immunolojik, pro-inflamatuar, anti-inflamatuar

INTRODUCTION

Headache may be the most common complaint of civilized human, with migraine and tension-type headache (TTH) comprising the bulk of this disorder. Though the pathophysiology of migraine is still unclear, different vascular, neurological, and neuro-inflammatory mechanisms have been proposed [15]. It is widely accepted that the intracranial throbbing pain of migraine is mediated primarily by neuronal activity along the trigeminovascular pathway. Activation and sensitization of primary afferent nociceptive neurons that innervate the intracranial meninges and their related blood vessels (i.e., meningeal nociceptors) is thought to be the first step in driving this sensory nociceptive system to promote the sensation of pain. While the exact mechanisms underlying activation and sensitization of meningeal nociceptors are not completely understood, local inflammation and release of mediators are thought to play a key role. Triggering mechanisms underlying these immune and neuronal responses are currently unknown [1,4,28,44].

Based on previous data the comorbidity between asthma and migraine is also other evidence supporting an immunological mechanism possibly related to the lowered thresholds of neurogenic inflammations. Alterations of several interleukins have previously been reported in migraineurs to further support an association between migraine and atopic disorders [6,14,22,34,36,39,41,48]. In other words, as a prototype of atopic disorder, asthma has been described as “pulmonary migraine” or “acephalic migraine”. Observational and laboratory evidence of intergenerational association has been found in hospital-based or case-control studies [10,17,41].

The local release of inflammatory molecules from degranulated mast cells (MC) during such neurogenic inflammation is believed to further stimulate meningeal nociceptors to promote a prolonged migraine headache. However, whether MC degranulation can promote such prolonged activation of meningeal nociceptors remains to be determined [29]. A short list of such MC mediators includes prostanoids, leukotrienes, cytokines, chemokines, and tryptase [33]. Among those, MC derived leukotrienes [47], the cytokines TNF-α and IL-6[45] and endothelin- 1[19] have been implicated in migraine pathophysiology.

In spite of the most supportive data about the possible association between migraine and atopic diseases, the real condition between the primary headache disorders and atopic disorders remains poorly understood. The main goal of this study

was to search the possible association between primary headache disorders and immunological determinants of atopic disorders during the headache attacks in a multicenter study design.

MATERIAL AND METHODS

Participants with headache were healthy except for the headaches and were recruited from 9 headache specialty clinics. The healthy volunteer control subjects were recruited from hospital workers and University students. Controls were considered completely headache-free and no-first degree relatives suffering from migraine.

The study protocol was approved by the Local Ethics Committee of Mersin University School of Medicine. The study conformed to Good Clinical Research Practice. All subjects gave written informed consent to the study protocol and detailed explanations were made according to the Helsinki declaration. Diagnoses of migraine and ETTH were made by ICHD 2nd edition criteria [21] and details were obtained by a semistructured questionnaire filled out by the co-investigators.

A total 146 patients (68.5%) with a diagnosis of migraine headache participated in this study. All patients underwent general physical and neurological examination. We carried out structured interviews concerning headaches, including detailed headache characteristics, associated symptoms, histories, and medications. Additionally, all patients were evaluated with a detailed structured questionnaire for allergy and asthma profile, including the presence of physician diagnosed of allergic diseases and migraine in family members. Among atopic disorders, asthma, rhinitis, conjunctivitis, seasonal allergy, food allergy and drug allergy were taken into consideration. Atopic disorders and asthma diagnosis was made as described in our previous report [41].

We excluded the patients taking prophylactic medication or with known inflammatory, infectious, or immune diseases. Subjects who had a history of therapy with nitrodilators or glucocorticoids in the last six months, a history of chronic liver or renal disease, haematological or autoimmune disorders, and systemic hypertension were also excluded from the study. Likewise, patients having chronic migraine and those with drug overuse were not included.

28 patients (13.1%) suffered from migraine with aura (MWA) and 118 (55.4%) from migraine without aura (MWoA). We also examined 38 (17.8%) subjects with episodic tension-type headache (ETTH) with same protocol indicated above. We recruited 29 (13.6%) healthy subjects without headache as controls (relating to low study budget the number of the controls should be kept limited). Patients were instructed to admit to the headache center for blood sampling as soon as possible at the onset of a typical migraine attack (max. 3 hours after the onset); consequently, patients living far from the center could not be included to this study. Nevertheless, the time of sample collection varied among patients. After blood sampling, patients were given their standard routine symptomatic medications for headache.

Blood samples (10 mL) were collected in tubes containing EDTA. They were centrifuged at 3000 rpm for 10 minutes and sera were stored at −80ºC until the determination of the analysis. The cold-chain transfer process was carried out strictly. IL-1β, IL-2, IL-6, IL-10 and TNF-α level were determined in sera samples using commercially available solid phase sandwich Enzyme Linked Immuno Sorbent Assay (ELISA) kits according to manufacturers' instructions (053001 for IL-1β, 054604 for IL-2, 055104 for IL-6, 054604 for IL-10 and 060402 for TNF-s, BioSource International, Nivelles/ Belgium) by ELISA (Biotek EL800/USA).

For each cytokine kit, there was no cross reactivity of monoclonal antibodies used for other cytokines. The optical density of each well was measured at 490 nm by an Immuno Reader J 2000. The detection limits were as follows: IL-1β < 1 pg/mL; IL-2 < 2 pg/mL; IL-6 < 0.8 pg/ mL; TNF-α < 2 pg/mL. Cut-off values of the mentioned variables as follows; IL-1β> 19.371 pg/ml, IL-2> 33.052 pg/ml, IL-6> 38,304 pg/ml, TNF- α> 61,210 pg/ml. IL-10 did not show any abnormal result in our study sample.

Serum was separated by centrifugation at 4000 rpm for 10 minutes and then sera was placed in polyethylene-sealed microtubes frozen at -80ºC until analysis. Serum total immunoglobulin measurements (including IgE, IgG and IgM levels) were determined by nephelometric methods (Backman coulter, USA) using special kits (Backman, USA kit numbers were M510275 for IgG, M511332 for IgE, M506078 for IgM). We tested both patient and control samples in each assay. The laboratory staff was blind to the clinical data.

In statistical analysis, the data was first evaluated using descriptive statistics. Patients with a history of atopic disorders were compared with others having cytokine and immunological screen abnormalities by appropriate statistical methods (Parametric data were compared using unpaired t test and nonparametric data were compared using the $\chi 2$ or Fisher exact tests). Factors related to having atopic disorders were investigated by regression analysis. Differences of clinical and immunological variables in patients with or without atopic disorders were assessed by parametric and non-parametric statistics, where appropriate according to their distribution. Pearson and Spearman correlation analyses were made between clinical and immunological parameters in the patient group, as appropriate. In order to investigate the effect of clinical and immunological variables on having a cytokine abnormality binary logistic regression analysis was also performed. Differences lower than 0.05% was accepted as significant.

RESULTS

The study included 213 subjects, 146 (68.5%) had migraine, 38 (17.8%) had ETTH and 29 (13.7%) were healthy controls. The mean age was 35.5±9.5 years (range 18–64 years) for migraine sufferers, 37.9±12.7 years (range 18–60 years) for ETTH sufferers and 31.6±6.7 years (range 24–51 years) for controls. Totally 153 (83.2%9) were female and 31 (16.8%) were male among headache groups. There were no significant age and sex differences between patient and control groups. The mean education time was 11.2±4.8 years for migraine, 11.3±5.1 years for ETTH sufferers and 15.4±3.1 years for healthy controls. They were commonly married (68.5% of migraineurs, 60.5% of ETTH groups and 55.2% of controls) and employed subjects. The mean disease duration from the headache diagnosis was 11.2±8.5 years for migraine group and 8.2±9.1 years for ETTH group (p>0.05). Details of the headache characteristics are presented in Table 1. The past medical histories showed high ratios of travel sickness and snorring in patients with migraine and high rates of hypertension, depression and anxiety disorders among patients with ETTH. Neurological examinations as well as neuroimaging were normal in all subjects.

A history of atopic disorders including asthma was observed in a total of 92 patients (43.2%); 11 patients (39.3%) with MwA, 59 patients (50.0%) with MwoA and 22 patients (57.9%) with ETTH. The most common atopic problems were allergic conjunctivitis, airway disorders including asthma, seasonal allergy and drug allergies in headache sufferers (Table 2). A positive family history of atopic disorders was reported more commonly in migraine sufferers compared to patients with ETTH (78.8% versus 21.2%,

p=0.004). None of the controls had a history of atopic disorders.

IL-2 and IL-6 levels were high both in migraine and ETTH patients but the abnormality was more evident in the migraine group. The number of the subjects with abnormal IL-1β and TNF-α levels was more common in migraine sufferers than in the ETTH group but this difference did not reach a statistical significance. On the other hand IgM abnormality was higher in ETTH group compared to migraineous subjects. IL-1β and TNF-α levels of migraine and ETTH sufferers can be seen in Figure 1. Other serological investigations did not show any significant differences among the groups (Table 3). There were also no significant differences in cytokine and immunglobuline levels between migraine sufferers with or without atopic disorders.

Spearmann correlaton analysis showed positive correlations between the following variables: headache duration and higher titres of IL-1β (CC: -0.19, p=0.016), frequency of the attacks and higher levels of IgE (CC: 0.20, p=0.015), atopic disorders of the patients and a positive family history for allergic disorders (CC: 0.19, p=0.007), the high levels of IL-1β and TNF-α (CC: 0.21, p=0.009), the high levels of IL-6 and TNF-α (CC: 0.37, p=0.000), and the high levels of IgM and IgG (CC: 0.30, p=0.000) among migraine sufferers. On the other hand there were significant correlations between the lower IL-2 levels and the high levels of TNF-α (CC: 0.47, p=0.000), the high levels of IL-6 and TNF-α abnormalities (CC: 0.69, p=0.000), and the high levels of IgM and IgG (CC: 0.36, p=0.023) among TTH sufferers (Table 4).

Significant results of the binary logistic regression analysis showed that only duration of headache has an important effect on having IL-2 abnormality (Exp-B: 0.322, 95% CI: 0.151-0.688, p=0.003) in patients with migraine. There was no important effect of clinical variables on serological abnormalitites or each other.

DISCUSSION

This study achieved important supportive data about the association between primary headache disorders and atopic disorders, based both on historical and laboratory data, using a multicenter attack study design. This study also supported the view that some shared relations between migraine and ETTH sufferers are far from a coincidence.

We also aimed to investigate the reliability of our previous supportive data about the association between primary headache disorders (especially migraine) and atopic disorders on clinical and laboratory basis. In order to exclude technical problems related to the sera transfer process, detailed information has been given to all investigators before the study. To the best of our knowledge, a similar attack based study, investigating the relationship between primary headache disorders and atopic disorders hasn't been reported before.

In a recent study, the relative risk of allergy in patients with migraine was found 1.59, while that for patients with respiratory symptoms consistent with asthma or with allergic eczematous contact dermatitis was 1.85 and 1.67, respectively [31]. Our study results showed 43.2% of the subjects included in the study reported a positive history of atopic disorders; however, it was unexpectedly common in ETTH sufferers. On the other hand a family history of atopic disorders was reported to be more common in migraine sufferers than ETTH. Our results support the thesis of migraine-TTH "spectrum" concept as previously mentioned [23,27]. We also found a clinical association between atopic disorders and not only with migraine but also with ETTH.

The known high rates of comorbidity between migraine and atopic diseases such

as eczema and asthma is an important argument for a suspected immune system dysfunction in migraineurs. The supportive evidence for the close association of migraine and atopic diseases was first recognized in 1983 [7,35,40,49,41]. Also the involvement of the immune system and migraine attacks was first mentioned over 80 years ago [55]. A number of papers reported higher plasma histamine levels that further increased during attacks in patients with a history of migraine [18,41,53]. Trigeminal activation and neurogenic inflammation is now a generally accepted model for migraine pathogenesis [3,16,29,42, 43]. Increasing evidence has led to the suggestion that brain mast cells may regulate vascular permeability in the brain [50]. Mast cells derive from a distinct precursor cell in the bone marrow, enter the brain from the leptomeninges and mature in the local microenvironment [26]. A more likely explanation is that meningeal mast cells are activated not only by allergic, but also by other, neuroimmune triggers. Mature mast cells vary considerably in their cytokine and proteolytic enzyme content [5]. In addition to vasodilatory molecules, mast cells secrete various pro-inflammatory mediators, such as kinins, prostaglandins, and numerous cytokines [52]. In addition to IgE and antigens, anaphylatoxins, cytokines, hormones, and neuropeptides can trigger mast cell secretion [51,53]. Recently, it is known that dural mast cells could promote headache by releasing 5-HT, PGI (2), and histamine[57]. Also another important experimental data supported that linking dural mast cell degranulation to prolonged activation of the trigeminal pain pathway believed to underlie intracranial headaches such as that of migraine[29]. On the other aspect, the unique mast cell protease tryptase causes microvascular leakage, as well as hyperresponsiveness of bronchi and neuronal hyperexcitability[20]. Based on this knowledge, the main topic of this study organised for a potential association between primary headache disorders, not only migraine but also TTH, and atopic disorders.

Cytokines are known to play an important role in inflammatory and pain conditions and they mediate both the communication between the different cells of the immune system and between the immune system and the brain[2,9,52,56]. They have been shown to induce headache, but few studies have examined cytokine levels in migraine patients. Both central and peripheral roles of proinflammatory mediators in the pathophysiology of migraine have been discussed in detail [47]. Although there are some conflicting results, these studies have shown a fluctuation of different circulating cytokine levels in primary headaches [25]. Recently, pro-inflammatory (IL-1β, IL-6, TGFß and TNFα), and anti-inflammatory cytokines (IL-10, IL-4, IL-13, and IL-2) have been shown to play a significant role in the modulation of pain threshold in migraine by contributing to the sensitization of trigeminal nerve fibers via by contribute to oedema and Aδ-fibre sensitization [8,9,11,12,24,25,37,38,39,45,54,56]. Even though some previous studies have investigated the possible role of TNF-α or other cytokines in migraine pathophysiology, no definite role was found [13,22,32,54]. In the current study, we have focused on ictal cytokine and immunglobuline changes in order to determine the inflammatory changes during headache attacks both in migraine and ETTH sufferers. We observed that almost all type of inflammatory markers. In the migraine group, lower levels of IL-2 were related with longer headache duration, shown by logistic regression analysis. We also showed some important correlations (see above) between cytokine

Table 1. The demographic and headache characteristics of patients with migraine and ETTH

	Migraine (n=146)	ETTH (n=38)	p
Age (years) (mean±SD)	35.5±9.5	37.9 ±12.7	ns
Diagnosis of headache (year)	11.2±8.5	8.2±9.1	ns
Duration of headache, n (%)			
Less than 4 hours	12 (8.2)	18 (47.4)	0.000
4 to 24 hours	75 (51.4)	15 (39.5)	
More than 24 hours	59 (40.4)	5 (13.1)	
Severity of headache, n (%)			0.000
Mild	-	3 (7.9)	
Moderate	32 (21.9)	24 (63.2)	
Severe	73 (50.0)	9 (23.7)	
Very severe	41 (28.1)	2 (5.3)	
Number of attacks *	4.4±3.4	6.8±4.3	0.000
Unilateral localization, n (%)	76 (52.1)	4 (10.5)	0.000
Quality of headache			0.000
pulsating	143 (97.9)	6 (15.8)	
pressing/dull	3 (2.1)	32 (84.2)	
Associated features of headache			0.000
nausea	125 (91.2)	6 (19.4)	
vomiting	49 (43.8)	-	
photophobia	124 (84.9)	11 (29.7)	
phonophobia	117 (84.2)	14 (42.4)	
Triggers of headache, n(%)			0.001
Stress	119 (81.5)	32 (84.2)	
Excersize	21 (14.3)	-	
Sleep disturbance	78 (53.4)	10 (26.3)	
Hunger	88 (60.2)	18 (47.3)	

Menstruel cycle	50 (34.2)	5 (13.1)	
Others	9 (6.1)	2 (5.2)	
Past medical history, n (%)**			0.041
None	54 (36.9)	9 (23.7)	
Travel sickness	54 (36.9)	9 (23.7)	
Snorring	27 (18.4)	6 (15.7)	
Hypertension	15 (10.2)	4 (10.5)	
Hyperlipidemia	11 (7.5)	3 (7.8)	
Depression	18 (12.3)	6 (15.7)	
Anxiety disorders	11 (7.5)	6 (15.7)	
Head trauma	5 (3.4)	4 (10.5)	
Positive family history of headache, n (%)	101 (69.2)	20 (52.6)	ns

* average frequency of attacks per month, in past years. ns: p>0.05

** some subjects had more than one comorbid medical condition.

ETTH: episodic tension type headache

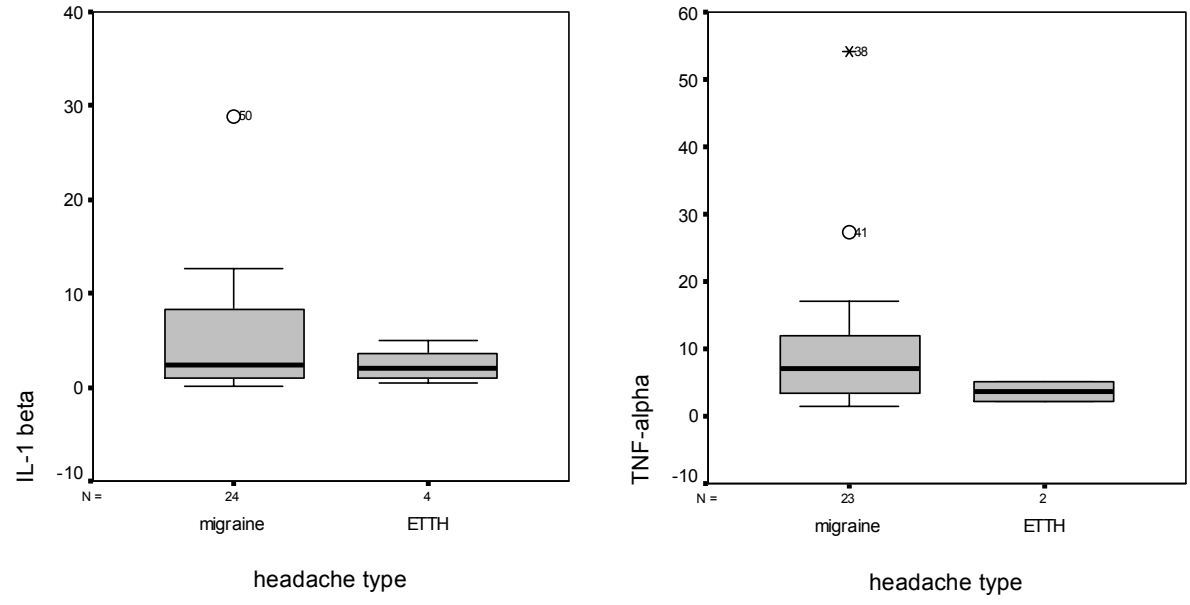

Figure 1. The distribution of IL 1-beta and TNF-alpha levels in headache groups.

Table 2. The reported frequencies of atopic disorders in patients with migraine and ETTH

	Migraine (n=146)		ETTH (n=38)		p
	Female	Male	Female	Male	
Number (%)*	123 (71.1)	23(28.9)	8 (21.1)	30 (78.9)	ns
No. of subjects with AD **, n(%)					ns
Asthma	11 (8.9)	-	2 (25)	-	
Rhinitis	9 (7.3)	1 (4.3)	1 (12.5)	1 (3.3)	
Conjunctivitis	13 (10.5)	3 (13.0)	4 (50)	1 (3.3)	
Seasonal allergy	14 (11.3)	2 (8.6)	2 (25)	1 (3.3)	
Food allergy	1 (0.8)	4 (17.3)	1 (12.5)	1 (3.3)	
Drug allergy	12 (9.7)	-	5 (62.5)	2 (6.7)	
Total	60 (48.8)	10 (43.5)	7 (87.5)	15 (50)	
Family history of atopic disorders, n (%)					
Asthma	14 (11.3)	1 (4.3)	4 (50.0)	1 (3.3)	
Rhinitis	11 (8.9)	3 (13.0)	1 (12.5)	-	
Conjunctivitis	4 (3.2)	-	2 (25)	1 (3.3)	
Others	5 (4.0)	3 (13.0)	1 (12.5)	1 (3.3)	

* figures in the brackets represents the percentage of the columns.

** some of the subjects reported coexistence multiple atopic disorders.

Table 3. The comparison of serological abnormalities among the study subjects

Parameters	**Migraine (n=146)**	**ETTH (n=38)**	**Controls (n=29)**
The number of atopic disorders, n (%)	70 (48.3)	22 (57.9)**	-
Positive family history of atopic dis., n (%)	41 (28.3)	11 (28.9)*	-
The number of IL-1-β abnormality, n (%)	24 (16.6)	4 (10.5)	1 (3.3)
The number of IL-2 abnormality, n (%)	29 (20.0)*	2 (5.3)	1 (3.3)
The number of IL 6 abnormality, n (%)	20 (13.8)*	1 (2.6)	1 (3.3)
The number of TNF-α abnormality, n (%)	23 (15.9)	2 (5.3)	2 (6.7)
The number of IgM abnormality, n (%)	1 (0.7)	3 (7.9)*	-
The number of IgG abnormality, n (%)	10 (6.9)	2 (5.3)	4 (13.3)
The number of IgE abnormality, n (%)	9 (6.2)	3 (7.9)	2 (6.7)

* $p<0.05$ and ** $p<0.001$

Table 4. The correlation analysis between headache variables and serological abnormalities

Parameters	Migraine	ETTH
IL-1-β abnormality	Duration of headache (CC:-0.19)*	-
	TNF-α abnormality (CC:0.21)**	
IL-2 abnormality	-	TNF-α abnormality (CC:0.47)**
		IgE abnormality (CC:0.36)*
IL 6 abnormality	TNF-α abnormality (CC:0.37)**	TNF-α abnormality (CC:0.69)**
TNF-α abnormality	PM	PM
IgM abnormality	IgG abnormality (CC:0.30)**	IgG abnormality (CC:0.36)*
IgG abnormality	PM	IgE abnormality (CC:036)*
IgE abnormality	-	PM

* $p<0.05$ and ** $p<0.001$, PM: Previously mentioned result

abnormalities and some clinical variables such as positive family history for allergic disorders, headache duration, atopic disorders of the patients, etc. both in subjects with migraine and ETTH. In this study we did not determine any IL-10 abnormalities. However, TNFα and IL-1β levels were significantly higher in migraine and TTH sufferers than healthy controls. There was also significant correlation between pro-inflammatory cytokine abnormalities, not likely being a coincidental finding. Our results suggested that ictal inflammatory changes are more common in migrainous and atopic subjects even though being not specific for migraine.

All studies investigating immunological parameters during a migraine attack found changes in various parameters[13,18,32]. However, a few studies demonstrated the importance of defining the accurate time of blood sampling [30,46]. In this aspect, our study achieves important data about the relation of blood sampling time and headache duration in a multicenter study design. We also determined a high rate of IgM abnormalities among ETTH sufferers, which have not been reported before. However in order to understand the exact clinical and pathophysiological meaning of our findings more comprehensive studies are needed.

Some limitations of this study warrant mention; we did not compare ictal and interictal cytokine levels. Also the low numbers of our healthy controls and ETTH sufferers are important limitations. Because of the low study budget we could not increase this numbers. We could not evaluate each of the subjects with atopic or non-atopic TTH separately because of the low number of the subjects included in this study for the mentioned reason. Also some additional data about basophils number and percentages in all patients groups (atopic and non atopic), PAF values etc. could be give us more informative data. Despite these limitations, this study has some implications;

- Clinical and laboratory correlates of migraine and atopic disorders have been demonstrated in a broad multicenter sample.
- Ictal cytokine abnormalities are more common in migraine sufferers than ETTH.

- Migraine and ETTH might share the same inflammatory mechanisms.

- Both in migraine and ETTH patients the ictal cytokine and immunglobuline abnormalities were clearly demonstrated and some clinical correlates have been determined.

In conclusion, our multicenter clinical and laboratory based study suggests that primary headache disorders (migraine and ETTH) are correlated with atopic changes and they might share the inflammatory mechanism (pro-inflammatory as well as anti-inflammatory cytokine abnormalities) during headache attacks.

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