Original Article

Prophylactic Drugs and Cytokine Levels in Migraineurs

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ABSTRACT

Background: There is considerable evidence suggesting that cytokines may play a role in mediating neurovascular inflammation associated with migraine headaches. Objective: To investigate plasma levels of pro- and anti-inflammatory cytokines in migraineurs and healthy controls and the relationship between these levels and clinical responses after prophylactic therapy. Methods: Fifty newly diagnosed migraine patients and 45 healthy controls were enrolled. Serum levels of pro-inflammatory (TNF-alpha and IL-6) and anti-inflammatory cytokines (IL-2, and IL-10) of migraineurs were investigated to determine the role of cytokines in migraine, and the relationship between these levels and clinical responses after prophylactic therapy with one or more of four drugs. Results: Migraineurs had significantly higher concentrations of TNF-α and IL-6 compared with controls (for TNF-α; 1.78±0.92 (ictally) and 1.06±0.50 pg/mL (interictally))vs. (0.64±0.60 pg/mL), *p*=0.003 and 0.008 respectively; for IL-6; 2.23±0.60 (ictally) and 1.17±0.49 pg/mL (interictally) vs. (0.57±0.51pg/mL), *p* =0.000 and 0.004, respectively .The mean IL-10 levels were found to be significantly lower in migraineurs (3.20±1.14 pg/mL (ictally) and 3.41±1.08pg/mL interictally)) than controls (5.92±1.19 pg/mL) (*p* =0.008 and 0.005). There were no difference in IL-2 levels between migraineurs and controls (0.14±0.12 (ictally) and 0.15± 0.13 pg/mL (interictally)) vs. (0.12±0.10 pg/mL) respectively Conclusion: Migraineurs had higher serum level of IL-6 & TNF-α and lower IL-10 levels than healthy individuals. These findings supported that cytokines may be involved in neurogenic inflammation and the pathogenesis of migraine. One of the potential mechanisms of actions of the migraine prophylaxis drugs might be related to their effects on different cytokines. **[Egypt J Neurol Psychiat Neurosurg. 2014; 51(1): 79-87]**

Key words: Migraine, Cytokine, Pathogenesis & Prophylactic drugs.

INTRODUCTION

Migraine is a chronic neurovascular disorder, characterized by episodic and disabling headaches with autonomic symptoms. Migraine affects 10-20% of the general population, affecting women up to four times more often than men. Although migraine is a long-known pathology accompanying mankind from the dawn of history, its pathogenesis remains unclear.[1,2]. There is a growing body of evidence to suggest that migraine and inflammation are linked, and often the term neurogenic inflammation is used. This idea is supported by the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) in migraine therapy as well as increased intracranial levels of inflammatory mediators during migraine attacks[3].

Earlier studies in individuals with migraine provided indirect evidence for the involvement of the immune system in migraine precipitation, including its association with atopic diseases such as eczema and asthma[4,5], the precipitation of migraine attacks during infections[6], and the elevated frequency of subclinical and clinical infections[7]. Several studies have also documented abnormalities in serum levels of complement proteins, immunoglobulins, histamine, cytokines, and immune cells in patients with migraine, however, the exact role that each of these changes play in the pathophysiology of migraine needs to be elucidated [8] . More recently, evidence indicates that cytokines may mediate pain associated with migraine [9].

Cytokines are small proteins produced by most cells in the body, which lead to multiple biologic activities that promote cell-cell interaction. Cytokines play an important role in several physiological and pathological settings, such as immunology, inflammation, and pain[10].

Cytokines are now considered the pain mediators in neurovascular inflammation. Activation and sensitization of meningeal nociceptors leads to afferent signaling that is thought to contribute to the headache that occurs during migraine [11]. However, the contributions of IL-6 to this process and the mechanisms by which this may occur have not yet been explored. Following acute IL-6 application, trigeminal ganglion neurons display phosphorylation of extracellular signal–regulated kinases (ERK) indicating that these neurons respond to IL-6 through activation of the Mitogen-Activated Protein Kinase (MAPK) signaling pathway [12].

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Activation of the ERK1/2 MAPK pathway has been implicated in induction and maintenance of various pain conditions via transcriptional, translational or post-translational regulation [13]. Recent work has identified the voltage-gated sodium channel Nav1.7 as a novel downstream post-translational target for MAPK. Nav1.7 is a threshold sodium channel expressed on small and medium dorsal root ganglion (DRG) neurons and inhibition of ERK1/2 decreased neuronal excitability by inhibiting Nav1.7 phosphorylation and altering its gating properties [14].

Some studies reported the increased levels of tumor necrosis factor alpha[15] and of interleukin-5 and interleukin-4 in migraine, whereas others reported no changes in plasma levels of tumor necrosis factor alpha, interleukin-1a, or interleukin-1b during migraine attacks[17]. The meaning of these data is generally interpreted as a possible immune dysfunction.

Because of different responses of cytokines, we investigated the levels of pro- and anti-inflammatory cytokines (TNF-α, IL-2, IL-6, and IL-10) in the serum of the migraine patients to understand the role of cytokines in migraine.

Aim of work:

This study was conducted to evaluate levels of the cytokines tumor; necrosis factor alpha, interleukin-2, and interleukin-6 and interleukin-10, and then to determine the relationship between these levels and clinical responses in patients with migraine after prophylactic therapy with one of four drugs.

PATIENTS AND METHODS

Study Design and Population

This is a case-control study of patients with migraine. The study group consisted of 50 patients who presented to the outpatient clinic of Kasr El Aini Hospital between January 2012 and May 2013, suffering from newly diagnosed migraine. Diagnosis was made using the criteria of the second edition of the International classification[18]. Mean age was 25.82±9.7 years. The male-to-female ratio was 21:29.

Inclusion criteria were migraineurs with indications for prophylaxis that were recurrent migraine attacks (at least 3 per month) that significantly interfered with daily activities (based on the headache history, including headache findings for frequency, severity, duration, and MIDAS (migraine disability assessment score) or PedMIDAS score) despite failure, overuse, or contraindication of acute therapy[19].

Exclusion criteria were recurrent migraine at a frequency of fewer than 3 per month that did not significantly interfere with daily activities; a medical history including the intake of prophylactic medication for migraine; history of hypertension, diabetes mellitus, stroke, renal disease, history of cardiovascular disease, inflammatory, infectious, or immune disease or abnormal C-reactive protein plasma levels.

All patients received a comprehensive neurologic examination and were also evaluated for complete blood count, liver and renal function, electrolytes, as well as electrocardiography and brain computerized tomography.

According to these criteria and based on the information in the relevant literature, children under 12 years of age were started on cyproheptadine (n = 5) at 0.2 mg/kg per day. Patients older than 12 years were started on amitriptyline (n = 6) at 0.5 mg/kg per day, or on propranolol (n = 8) at 10-40 mg/day), or on topiramate (n = 9) at 50–100 mg/day in two divided doses[20,21]. A patient with unsatisfactory response to prophylactic monotherapy after two months, a second suitable drug was added (n = 22). All patients completed the 4-month treatment. Treatment response was evaluated with the MIDAS or PedMIDAS instrument[22,23].

The control group included 45 healthy participants without the history of headache, with a negative history of vascular diseases, hypertension, diabetes mellitus, renal impairment, infectious and/or autoimmune diseases. Mean age was 26.91±8.6 years. The male-to-female ratio was 19:26.

Serum levels of pro-inflammatory (TNF-alpha and IL-6) and anti-inflammatory cytokines (IL-2, and IL-10) of migraine patients were investigated. Blood sampling was performed within 2-6 h from the onset of migraine headache. Two days after pain termination, the headache-free measurements were analyzed, and under the same conditions in controls. Serum levels of the cytokines were measured 4 months after the prophylactic treatment. Each collected blood sample was immediately centrifuged at 4000 rpm +4°C for 10 min and then transferred into an Eppendorf tube. Serum was stocked at –80°C for not more than 15 days. TNF alpha, IL-2, IL-6 and IL-10 levels were measured using a chemiluminescent enzyme-immunometric assay (IMMULITE Automated immunoassay system; Immulite DPC, Los Angeles, CA, USA).

Statistical Methods

All statistical analyses were performed using SPSS, version 21, for Windows (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± standard deviation. The normality of the distribution for all variables was assessed by the Kolmogorov–Smirnov test. Student's t-test was used for normally distributed variables. Mann-Whitney U-test was used for non-parametric variables. P values less than 0.05 were considered statistically significant, and less than 0.01 were considered highly significant.

RESULTS

Mean age of the migraine patients was 25.82±9.7 years (8-45 years). Migraine group consisted of 21 men and 29 women. Mean age of the control group was 26.91±8.6 years (10-48 years).The control group comprised of 19 men and 26 women. No differences were found in mean age and gender distribution between the migraine and the control groups (p>0.05). Age of onset of migraine ranged from age 7.5 years to 38 years with a mean of 22.6 years with a SD of 8.1 years, Duration of migraine since onset to date of inclusion in this study ranged from 0.5 to 7 years with a mean of 3.2 and SD of 1.9 years. The MIDAS score in patient ranged from 9 to 35 with a mean of 18.4 and SD 6.6.

Comparing migraine patients with healthy controls, we found that migraine patients had significantly higher concentrations of ictal and interictal TNF-α and IL-6 compared with the healthy controls (p<0.01). IL-10 levels were found significantly lower in migraineurs than controls (p<0.01). There were no differences in IL-2 levels between patients with migraine and healthy controls (p>0.05). After 4 months, there were no differences in the measured cytokines between migraine patients and healthy controls except IL-10 that was significantly lower in migraineurs (Table 1).

Comparing the three measured levels of cytokines in migraineurs, we found significant difference within levels of TNF-α and IL-6, being lowest after 4-month prophylactic treatment. For IL-2, the ictal level was significantly lower than after 4 months level. For IL-10, the ictal level was significantly lower than interictal and after 4 months levels (Table 2).

There was no significant difference between the common migraine and classic migraine as regard the measured level of the examined cytokines (Table 3).

Comparing patients older than 20years, we refer to them as adult with those younger than 20 years, referring to them as children; the only significant difference was between the levels of interictal IL-6, being lower in children group (Table 4).

After 4-months treatment, the used drugs either individually or in combination, reduced the levels of TNF-α and IL-6 with no significant effect on IL-2 or IL-10 (Table 5).

There was a statistically significant positive correlation between the three measured serum levels of IL-6 and illness duration, age of migraine patients. The ictal and after 4-months treatment IL-6 level was also positively correlated with the corresponding MIDAS or PedMIDAS score. On the other hand, the interictal IL-10 level was negatively correlated with the corresponding MIDAS/ PedMIDAS score and the duration of migraine.

Table 1. Comparison between healthy controls and migraine patients as regards the serum level of cytokines.

		Migraine (n=50)		Control (n=45)		P1-value
		Mean	SD	Mean	SD	
TNF-α (pg/mL)	Ictal	1.78	0.92	0.64	0.60	0.003*
	Interictal	1.06	0.50			0.008*
	After treatment	0.41	0.30			0.30
IL-6 (pg/mL)	Ictal	2.23	0.60	0.57	0.51	0.000*
	Interictal	1.17	0.49			0.004*
	After treatment	0.53	0.40			0.10
IL-2 (pg/mL)	Ictal	0.14	0.12	0.12	0.10	0.50
	Interictal	0.15	0.13			0.35
	After treatment	0.17	0.15			0.08
IL-10 (pg/mL)	Ictal	3.20	1.14	5.92	1.19	0.008*
	Interictal	3.41	1.08			0.005*
	After treatment	3.40	1.09			0.003*

* Significant at P<0.01

Table 2. Comparison between different levels of cytokines in migraine patients.

		Migraine (n=50)		P-value
		Mean	SD	
TNF-α (pg/mL)	Ictal	1.78	0.92	0.007*
	Interictal	1.06	0.50	
	After treatment	0.41	0.30	
IL-6 (pg/mL)	Ictal	2.23	0.60	0.000*
	Interictal	1.17	0.49	
	After treatment	0.53	0.40	
IL-2 (pg/mL)	Ictal	0.14	0.12	†
	Interictal	0.15	0.13	
	After treatment	0.17	0.15	
IL-10 (pg/mL)	Ictal	3.20	1.14	‡
	Interictal	3.41	1.08	
	After treatment	3.40	1.09	

*all levels were significantly different from each other (P<0.01)
†For IL-2: P for difference between ictal and interictal 0.65 (non significant), P for difference between interictal and after 4 months measurement 0.24 (non significant) and P for difference between ictal and after 4 months measurement 0.04 (significant).
‡For IL-10: P for difference between ictal and interictal 0.02 (significant), P for difference between interictal and after 4 months measurement 0.88 (non significant) and P for difference between ictal and after 4 months measurement 0.01 (significant).

Table 3. Comparison between common migraine and classic migraine patients as regards the serum level of cytokines.

		Migraine (n=50)				P-value
		Without aura (n=35)		With aura (n=15)		
		Mean	SD	Mean	SD	
TNF-α (pg/mL)	Ictal	1.84	1.00	1.63	0.69	0.46
	Interictal	1.05	0.52	1.06	0.45	0.97
	After treatment	0.42	0.31	0.40	0.28	0.85
IL-6 (pg/mL)	Ictal	2.26	0.62	2.16	0.55	0.59
	Interictal	1.25	0.47	0.98	0.49	0.07
	After treatment	0.58	0.39	0.41	0.40	0.17
IL-2 (pg/mL)	Ictal	0.12	0.07	0.18	0.18	0.16
	Interictal	0.15	0.13	0.15	0.11	0.95
	After treatment	0.14	0.11	.25	0.20	0.06
IL-10 (pg/mL)	Ictal	3.16	1.14	3.31	1.16	0.68
	Interictal	3.25	1.10	3.79	0.98	0.11
	After treatment	3.33	1.14	3.56	0.98	0.58

Table 4. Comparison between children and adults as regards the serum levels of cytokines.

		Migraine (n=50)				P-value
		Children (n=13)		Adults (n=37)		
		Mean	SD	Mean	SD	
TNF-α (pg/mL)	Ictal	1.49	0.71	1.88	0.97	0.20
	Interictal	1.00	0.41	1.07	0.53	0.65
	After treatment	0.43	0.31	0.41	0.30	0.79
IL-6 (pg/mL)	Ictal	2.08	0.38	2.28	0.65	0.195
	Interictal	0.76	0.16	1.32	0.48	0.005*
	After treatment	0.14	0.12	0.66	0.37	0.849
IL-2 (pg/mL)	Ictal	0.19	0.20	0.12	0.07	0.285
	Interictal	0.16	0.11	0.14	0.13	0.749
	After treatment	0.18	0.17	0.17	0.14	0.889
IL-10 (pg/mL)	Ictal	2.80	0.87	3.34	1.20	0.09
	Interictal	3.25	0.70	3.46	1.19	0.444
	After treatment	3.26	0.67	3.45	1.21	0.499

* Significant at P<0.01

Table 5. Serum cytokines levels migraine patients before and after treatment with one or more of four drugs for migraine.

		Before treatment		After treatment		P-value
		Mean	SD	Mean	SD	
Propranolol (n=8)	TNF-α (pg/mL)	1.05	0.36	0.49	0.32	0.000**
	IL-6 (pg/mL)	1.13	0.62	0.43	0.48	0.000**
	IL-2 (pg/mL)	0.15	0.06	0.18	0.11	0.461
	IL-10 (pg/mL)	3.72	1.03	3.69	1.08	0.579
Amitriptyline (n=6)	TNF-α (pg/mL)	1.32	0.63	0.62	0.53	0.004**
	IL-6 (pg/mL)	1.13	0.57	0.43	0.26	0.006**
	IL-2 (pg/mL)	0.19	0.18	0.15	0.10	0.702
	IL-10 (pg/mL)	4.52	0.66	4.50	0.66	0.853
Topiramate (n=9)	TNF-α (pg/mL)	0.98	0.51	0.39	0.27	0.001**
	IL-6 (pg/mL)	0.83	0.13	0.31	0.34	0.001**
	IL-2 (pg/mL)	0.12	0.09	.23	0.21	0.138
	IL-10 (pg/mL)	3.52	1.11	3.39	1.07	0.551
Cyproheptadine (n=5)	TNF-α (pg/mL)	0.91	0.49	0.28	0.16	0.029*
	IL-6 (pg/mL)	0.69	0.12	0.09	0.06	0.000**
	IL-2 (pg/mL)	0.18	0.17	0.22	0.26	0.453
	IL-10 (pg/mL)	3.32	0.98	3.18	1.01	0.357
Polytherapy (n=22)	TNF-α (pg/mL)	1.05	0.52	0.37	0.24	0.000**
	IL-6 (pg/mL)	1.45	0.39	0.78	0.31	0.000**
	IL-2 (pg/mL)	0.14	0.13	0.14	0.11	0.832
	IL-10 (pg/mL)	2.96	1.01	3.04	1.06	0.419

* Significant at P<0.05 ** Significant at P<0.01

Table 6. Correlation between different levels of cytokines and age of onset, duration of migraine and MIDAS/ PedMIDAS scores in migraine patients.

		Age of onset		Duration of migraine		MIDAS/ PedMIDAS	
		r-value	P-value	r-value	P-value	r-value	P-value
TNF-α	Ictal	0.126	0.384	0.078	0.591	0.013	0.927
	Interictal	0.002	0.991	-0.215	0.133	-0.026	0.858
	After treatment	- 0.114	0.430	-0.278	0.051	-0.015	0.917
IL -6	Ictal	0.311	0.028*	0.414	0.003**	0.384	0.006**
	Interictal	0.435	0.002**	0.452	0.001**	0.232	0.105
	After treatment	0.482	0.000**	0.548	0.000**	0.282	.047*
IL-2	Ictal	-0.204	0.155	-0.246	0.085	-0.156	0.278
	Interictal	-0.080	0.582	-0.051	0.724	-0.069	0.635
	After treatment	0.002	0.991	-0.160	0.266	-0.212	0.139
IL-10	Ictal	-0.032	0.825	-0.218	0.129	-0.119	0.411
	Interictal	-0.223	0.119	-0.351	0.012*	-0.311	0.028*
	After treatment	-0.120	0.406	-0.247	0.084	-0.239	0.094

* Significant at P<0.05** Significant at P<0.01

DISCUSSION

Cytokines are polypeptide or glycopeptide molecules produced by most cells in the body, which lead to multiple biologic activities to facilitate cell-cell interaction. Several lines of evidences suggest that cytokines play a role in several physiological and pathological settings such as immunology, inflammation and pain[24].

Cytokines have been shown to induce headache and many studies have examined cytokines levels in migraine patients but the results were very controversial. One reason that could explain the controversial data could be that the cytokine assays have been measured in many cases only in the peripheral blood, in some cases during the attack and in others interictally[25].

Pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1b, interleukin-6, and anti-inflammatory cytokines such as interleukin-10, interleukin-4, interleukin-3, and interleukin-2 have been reported to play a significant role in the modulation of pain threshold and they could contribute to trigeminal nerve fibers sensitization[26].

In our study, we found a statistically significant difference between ictal and interictal serum level of IL-6 & TNF-α in migraine patients in comparison to the control, both were higher in the patient group (p<0.01). The present results are generally in agreement with previous data. Uzar et al. stated that migraine patients had significantly higher concentrations of and IL-6 as compared to the healthy controls[27]. Regarding TNF-α, most studies indicate that TNF-α plasma levels increase during migraine attack and also are higher in migraineurs between attacks[15,28,29]. Furthermore, in clinical trials TNF-α has been demonstrated to induce headache, and TNF-α antibodies can reduce pain in humans [30]. On the other hand, Fidani et al. in a study carried out in migraine patients during attacks and in attack-free periods did not found a significant difference in the serum level of and TNF-α as compared to the control group[24]. Also, Uzar et al. found no differences in TNF-α level between patients with migraine and healthy controls[27].

Originally, IL-10 described as a cytokine synthesis inhibitory factor, it has major down-regulatory influences on inflammation. The expression of IL-10 by antigen-presenting cells may have a role in attenuating inflammation through this ability to inhibit synthesis of nonspecific proinflammatory cytokines, such as IL-1, IL-6, and TNF- α□□□. In our study, We found a significantly lower serum IL-10 levels that measured at three occasions in migraine patients compared with healthy controls (p<0.01). This is in accordance with Uzar et al., who found that IL-10 levels were significantly lower in migraineurs as compared to the controls[27]. In contrary, Munno et al. reported that the patients during migraine attacks had higher levels IL-10 compared to the healthy control[32].

IL-2 is normally produced in the body during an immune response. IL-2 drives the proliferation and differentiation of T cells, which have a central role in the adaptive immune system. IL-2 is related to

lymphocyte activation and usually involved in inflammation due to viral etiology[33]. No statistically significant difference between ictal, interictal level of IL-2 (anti-inflammatory cytokine) & its level 4 months after prophylactic treatment in migraine patients and the levels of the controls. These results are in line with Fidani et al. & Uzar et al., who stated that no statistically significant difference in the serum level of IL-2 during attacks and in attack-free periods compared to those in healthy control[24,27]. In contrary, Shimomura et al. reported decreased serum IL-2 level in patients with migraine compared to healthy control[34]. Our finding, in addition to others findings suggested that neuroinflammation in migraine pathogenesis may be related to cytokines other than IL-2.[27]

In our study, there was a statistically significant difference between ictal, interictal serum levels of IL-6 and TNF-α among migraine patients being highest during the attack. This is matched with the findings of Covelli et al. and Gallai et al.[15,29] but in contrary to Perini et al. who found no differences in IL-6 levels of patients outside and during the migraine attacks[28].

In the present study there were no statistically significant difference regarding serum levels of ictal, inerictal , level measured 4 months after prophylactic treatment of IL-6, TNF-, IL-2 and IL-10 between migraine patients with aura and patients without aura except for IL-2 measured 4 months after prophylactic treatment being higher in patients with aura. This is in accordance with Uzar et al., Perini et al. and Empl et al. who found no statistically significant difference in the levels of TNF-α, IL-2, IL-6 and IL-10, in patients with migraine with aura compared to the patients with migraine without aura[27,28,34]. However, Boc´kowski et al. found that TNF- α level was increased in migraine patients with aura subgroup, as compared to those without aura but the difference was not statistically significant [35].

In this study, when we compared the adults' serum levels of the examined cytokines with those of children, the only significant difference was between the levels of interictal IL-6, being lower in children group. This could be explained by long medical history of migraine in adult patients and frequent intake of analgesic drugs[36].

The presence or the absence of aura did not make any significant difference between the cytokine profile of patients with aura and those without aura. This is unlike Boc´kowski et al and Kaciński et al. who found that cytokine profile of migraineurs with or without aura is not identical, but their patient were restricted to childhood age[35,37].

Cyproheptadine (an antihistaminic and antiserotonergic), amitriptyline (a tricyclic antidepressant), propranolol (a serotonin receptor blocker) and topiramate (antiepileptic) have been the most widely used prophylactic agents in children with migraine[38].

In our study, the used four drugs either separately or in combination significantly reduced TNF-α and IL-6 levels. This go in line with Hirfanoglu et al. who found that levels of TNF-α and IL-6 levels significantly decreased after treatment with cyproheptadine, compared with levels before treatment in migraine patients[39]. Also Gallai et al. stated that, TNF-α level have been found to decrease after 2 months of amitriptyline therapy[29]. However, Abdulkadir et al. found that the serum concentration of IL-6 in chronic migraine patients with a history of TPM use did not differ significantly from the concentration in chronic migraine patients who did not use topiramate[40].

In this study, correlation between the measured levels of cytokines and the clinical features of migraineurs revealed significant positive correlation between the three measured serum levels of IL-6 and illness duration, age of migraine patients. The ictal and after 4-months treatment IL-6 level were also positively correlated with the corresponding MIDAS or PedMIDAS score. Unlike Boc´kowski et al. and Munno et al., who found no correlation between IL-10 level and clinical features, such as duration of illness and age of migraineurs we found that the interictal IL-10 level was negatively correlated with the corresponding MIDAS/ PedMIDAS score and the duration of migraine [41,42]. This can be explained with different clinical features of the studied patients, in our study we only selected patients with migraine that significantly interfered with their daily activities.

Conclusion

Migraineurs had higher serum level of IL-6 & TNF-α (Pro-inflammatory cytokines) and lower level of IL-10 (Anti-inflammatory cytokines) than healthy individuals. These findings supported that cytokines may be involved in neurogenic inflammation and may be related to the pathogenesis of migraine. One of the potential mechanisms of actions of the drugs used in migraine prophylaxis might be related to their effects on different cytokines.

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الملخص العربي

العقاقير الواقيه ومستوى السيتوكينات فى مرضى الصداع النصفى

أجريت هذه الدراسة على خمسين من مرضى الصداع النصفي المحتاجين للعلاج الوقائى بالاضافه الى مجموعة ضابطة من خمسة وأربعين من الأصحاء. و قد تم فحص المرضى سريريا وأجريت لهم أشعه مقطعيه للمخ وأبحاث معمليه تشمل المعامل الروتنيه. تم عمل نسبة أمصال دلالات الالتهاب (انترلوكين ٦و٢و ١٠ و معامل نخر الورم –ألفا) للمجموعة الضابطة وللمرضى خلال النوبة و ما بين حدوث النوبات وبعد ٤ أشهر من العلاج الوقائي بعقار أو أكثر من أربع عقاقير واقيه من نوبات الصداع النصفي : السيبروهبتادين ,البروبرانولول ,امتيربتايلين والتوبيرامیت.وتمت متابعة نتيجة العلاج بمقياس تقدير اعاقة الشقيقه للكبار أو للأطفال

وقد توصلت الدراسة للنتائج التالية:

١. زيادة نسبة مصل دلالات الالتهاب (انترلوكين –٦ و معامل نخر الورم – ألفا) في المرضى الذين يعانون من الصداع النصفي التى تم تقييمها خلال النوبة و ما بين حدوث النوبات عن المجموعة الضابطة
٢. زيادة نسبة مصل (انترلوكين –١٠) في المجموعة الضابطة عن المرضى الذين يعانون من الصداع النصفي سواء خلال النوبة او ما بين حدوث النوبات و بعد ٤ أشهر من العلاج الوقائي
٣. لايوجد فروق ذات دلالة إحصائية في مستوى مصل انترلوكين –٢ بين المرضى الذين يعانون من الصداع النصفي و المجموعة الضابطة
٤. أدى تناول المرضى للعقاقير الواقيه من نوبات الصداع النصفي الى انخفاض ملحوظ إحصائيا في مستوى (انترلوكين –٦ و معامل نخر الورم – ألفا).