Cerebrovascular reactivity and neurogenic inflammation in migraine

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Background The exact mechanism of migraine is still unknown; however, it is believed to be a neurovascular disorder, where the cerebral vascular reactivity is malfunctioning. Although several studies have found alterations in velocity of blood flow and in cerebral vasomotor reactivity of intracranial arteries in migraineurs in headache-free periods, as well as during migraine attacks, the results are inconclusive. Another theory of migraine is the neurogenic inflammation involving the release of various vasoactive neuropeptides, which evoke a cascade of events that have a role in migraine attacks.

Aim of work To evaluate the role of both vascular and inflammatory theories in migraine with and without aura.

Objective The objective of this study was to examine the cerebrovascular reactivity to repetitive flash stimulation during interictal period of migraine and determine the serum levels of transforming growth factor β-1 (TGFβ-1) as an inflammatory mediator in migraine with and without aura.

Patients and methods The changes in peak systolic volume (PSV) of both middle cerebral and posterior cerebral arteries in response to repetitive flash stimulation were evaluated by transcranial Doppler in 35 migraineurs (23 patients with aura and 12 without aura), during interictal period, and in 25 age-matched and sex-matched apparently healthy control participants. Moreover, serum levels of TGFβ-1 were determined in both the patients and control participants.

Results The middle cerebral artery in migraineurs shows significant increase in PSV after flash stimulation in comparison with control participants who showed a habituation in PSV levels in response to stimulation. In posterior cerebral artery, compared with normal participants, migraineurs showed significant increase in PSV measures and PSV changes at the beginning and after the end of stimulation. The lack of habituation is significantly pronounced in patients with migraine with aura, in comparison with those without aura. Regarding TGFβ-1 serum levels, they were significantly higher in migraineurs than control participants. Moreover, patients with migraine without aura show significantly higher serum levels of TGFβ-1 in comparison with patients with migraine with aura.

Conclusion Lack of habituation of the cerebrovascular response in migrainers might contribute to a disturbance in the metabolic homeostasis of the brain that might induce migraine attacks. Neurogenic inflammation has a role in migraine attacks.

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Introduction

Migraine is a disabling neurovascular disorder that affects ~12% of general population, and in approximately one-third of these patients, migraine attacks are preceded by neurological symptoms associated with a transient cortical malfunction, collectively known as aura [1].

Because of the complexity of this disorder, which is not only limited to its multifactorial origin but also includes remarkable premonitory symptomatology, it is thought that migraine headache is a manifestation of a brain state of altered excitability capable of activating the trigeminovascular system in genetically susceptible individuals [2].

The neuronal hypersensivity to different intrinsic and extrinsic stimuli is the primary pathophysiological changes in the migraine. The migraineurs show a reduced adaptation to environmental stimuli owing to no habituation in contrast with healthy controls. These features might also be transmitted to the cerebral vasoreactivity [3].

In electrophysiological trials of migraine, patients showed absent habituation or even a potentiation of the response to repetitive stimuli [4].

The absence of habituation has been interpreted as a dysfunction of the cortical information processing. It seems to be more pronounced in the interictal phase and tends to normalize just before and during the migraine attack [5].

Moreover, changes in the diameter of intracranial arteries might have a major role in the pathophysiology of migraine. Although several studies have found alterations in velocity of blood flow and in cerebral vasomotor reactivity of intracranial arteries in

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migrainuers in headache-free periods, as well as during migraine attacks, the results are inconclusive [6].

In recent years, transcranial Doppler (TCD) has been used to evaluate cerebral blood flow velocity (CBFV) changes in patients with migraine, during and between attacks [7].

Another theory of migraine, the neurogenic inflammation, points to aseptic inflammation as a major element in migraine attack. Neurogenic inflammation involves the release of various vasoactive neuropeptides from trigeminal and parasympathetic perivascular fibers, which evoke a cascade of events characterized by vasodilation, plasma protein extravasation, and the release of proinflammatory mediators [8].

Transforming growth factor β-1 (TGFβ-1) was considered to have a role in inflammation. TGFβ-1 is a polypeptide member of the TGFβ super-family of cytokines. It is a secreted protein that is involved in many cellular functions, including the control of cell growth, cell proliferation, cell differentiation, apoptosis, and inflammation. TGFβ-1 was evaluated in patients with migraine, and it has been reported that TGFβ-1 might have a role in migraine pathogenesis [9].

In this study, we tried to evaluate the role of both vascular and inflammatory theories in migraine with and without aura, for better understanding of this disabling, complex neurological disorder, hoping for better management.

Patients and methods

Sixty patients were included in this study, with age ranged from 20 to 50 years. Thirty-five patients with migraine were selected from the neurology outpatient clinic of Al Zahraa University Hospital, according to Headache Classification Committee of the International Headache Society (HIS) diagnostic criteria [10]. The patients were divided into two subgroups: 12 patients with migraine with aura and 23 patients without aura. The control group consists of 25 apparently healthy participants, who were age and sex matched with the patients.

Study design

Case/control (comparative) study

Patients with hypertension, diabetes, or history of medical systemic, neurological, or psychiatric illness (e.g. stroke and vasculitis), those with other types of headache, and those on prophylactic treatment of migraine were excluded from the study.

Patients underwent full history taking including type of headache, frequency of headache attacks per month, and general and neurological examination.

All patients (during interictal period) and controls were subjected to the following:

Laboratory investigations

Laboratory investigations included the following:

(1) Routine laboratory investigations.
(2) Serum transforming growth factor beta-1.

Serum transforming growth factor β-1 determination

TGFβ-1 determination was performed using ELISA (Komabiotic, catalog no K0332110), according to the manufacturer's instructions.

Transcranial Doppler study

TCD study was done using a Wakie French 1TC ultrasound Doppler instrument via transtemporal window.

Procedure

The patient was placed supine on the examining table, and we tried to make the auditory and sensory stimulus to minimal level. Ultrasound gel was applied to the skin above temporal window.

TCD was performed during interictal period of migraine in all patients using a 2-MHz probe of a color-coded ultrasound system. It was used in a standard transtemporal approach to analyze peak systolic velocity (PSV) in the middle cerebral artery (MCA), and posterior cerebral artery (PCA) on both sides.

During sonation of MCA and PCA, photo stimulation with the lamp of IP55 was done binocularly. Flickering light in 100 s from the distance of ~1 m was exposed to the participants. The PSV was recorded before, during, and after stimulation. PSV values were measured along full segment of each MCA and PCA. In this study, we select the highest PSV value detected from several measurements.

Statistical analysis

Data were analyzed using statistical program for social science, version 18.0. Quantitative data were expressed as mean±SD. Qualitative data were expressed as frequency and percentage.

The following tests were done:

(1) Independent-samples t-test of significance was used when comparing between two means.
(2) χ^2-test of significance was used to compare proportions between two qualitative parameters.
(3) Pearson's correlation coefficient (r) test was used for correlating data.
(4) Probability (P-value)
    (a) P-value less than 0.05 was considered significant.
    (b) P-value less than 0.01 was considered as highly significant.
    (c) P-value more than 0.05 was considered insignificant.

Results

Characteristics of the study population

This study included 35 patients with migraine, with 20 (57.1%) females and 15 (42.9%) males, and 25 control participants, with 13 (52.0%) females and 12 (48.0%) males. The mean age in the patients group was 37.49±7.85 years, and the mean age of the control group was 36.17± 11.40 years.

There were no statistically significant differences between the two groups regarding the demographic data.

The patients group were divided into two groups – 12 patients with migraine with aura and 23 patients with migraine without aura – with no statistically significant differences between the two groups regarding age, sex, duration of headache, and frequency of headache attacks per month (P>0.05) (Table 1).

Results of transcranial Doppler

Cerebrovascular response of middle cerebral artery in migraineurs and control participants

There were no significant differences in PSV of MCA between patients and controls at baseline or during flash stimulation (P>0.05).

However, after the end of stimulation, there was a significant increase in PSV of MCA in migraineurs than in controls (Table 2).

Table 1 Comparison between patients subgroups regarding demographic data and duration and frequency of headache

	Without aura (n=23)	With aura (n=12)	Independent t-test	
			t	P-value
Age				
Mean±SD	36.04±8.39	40.25±6.09	1.535	0.134
Range	20–50	31–50		
Sex [n (%)]				
Female	13 (56.5)	7 (58.3)	0.011	0.918
Male	10 (43.5)	5 (41.7)		
Duration of headache [n (%)]				
Mean±SD	7.91±5.38	10.25±5.14	1.239	0.224
Range	2–20	4–20		
Frequency of headache per month				
Median (IQR)	12 (10–16)	16 (13.5–20)	–1.298*	0.194
Range	4–30	8–30		

IQR, interquartile range. *Means statistically significant.

Table 2 Comparison between patients and control group regarding peak systolic volume of middle cerebral artery and posterior cerebral artery (before, during, and after flash)

	Control group (n=25)	Patients group (n=35)	Independent t-test	
			t	P-value
MCA (PSV) before				
Mean±SD	52.50±3.99	59.20±13.18	–1.723	0.092
Range	44–57	30–84		
MCA (PSV) during				
Mean±SD	63.25±5.07	67.23±14.60	–0.919	0.363
Range	55–70	40–90		
MCA (PSV) after				
Mean±SD	63.92±3.53	70.17±6.46	–3.178	0.013*
Range	56–69	58–85		
PCA (PSV) before				
Mean±SD	39.00±6.05	65.54±12.80	6.887	0.003*
Range	29–49	39–100		
PCA (PSV) during				
Mean±SD	47.17±5.80	71.63±14.60	5.620	0.005*
Range	38–58	42–112		
PCA (PSV) after				
Mean±SD	45.58±7.00	75.46±12.16	8.030	0.002*
Range	32–55	46–110		

MCA, middle cerebral artery; PCA, posterior cerebral artery; PSV, peak systolic volume. *Means statistically significant.

Regarding PSV changes of MCA (differences before and after flash stimulation), there was no significant difference between patients and control group (Table 3).

Cerebrovascular response of posterior cerebral artery in migraineurs and control participants

The PSV changes of PCA were significantly higher in the migraineurs than in controls at baseline, during, and after flash stimulation ($P<0.05$) (Table 2).

Moreover, PSV changes of PCA (differences before and after flash stimulation) were significantly higher in patients than in control group (Table 3).

Transcranial Doppler results in patient subgroups (migraine with and without aura)

There is a statistically significant difference between two patient subgroups regarding PSV of PCA after flash stimulation, being higher in those with migraine with aura (Table 4). Moreover, there is a statistically significant difference between two patient subgroups regarding PSV changes of PCA, being higher in migraine with aura (Table 5).

Regarding MCA, no statistically significant difference between two patient subgroups regarding PSV of MCA before, during, and after flash stimulation (Table 4), or significant changes between two patient subgroups regarding PSV changes (differences between before and after stimulation), of MCA (Table 5).

Results of serum levels of transforming growth factor β-1

There is a highly statistical significant difference between patients (202.27±28.73) and control (46.22± 7.75) groups regarding TGFβ-1, being higher in patients than in control (Fig. 1).

Table 3 Comparison between patient and control regarding peak systolic volume changes (difference before flash and after flash stimulation)

	Control group (*n*=25)	Patients group (*n*=35)	Ma–n-Whitney test	
			Z	*P*-value
PSV changes in MCA				
Median (IQR)	7.5 (6–9)	9 (8–12)	2.176	0.070
Range	5–10	4–19		
PSV changes in PCA				
Median (IQR)	5.5 (4–7)	9 (7–12)	2.807	0.005*
Range	3–14	4–18		

IQR, interquartile range; MCA, middle cerebral artery; PCA, posterior cerebral artery; PSV, peak systolic volume. *Means statistically significant.

Moreover, there is a statistically significant difference between two patient subgroups regarding TGFβ-1, being higher in migraine without aura (214.91± 24.34) (Fig. 2).

There is a statistically significant positive correlation between TGFβ-1serum levels and duration of headache and frequency of headache attacks per month (Table 6).

Discussion

It has been suggested that the pathogenesis of migraine is related to an imbalance in the activity between the brain stem nuclei regulating antinociception and the

Table 4 Comparison between two patient subgroups regarding transcranial Doppler findings

PSV	Without aura (*n*=23)	With aura (*n*=12)	Independent *t*-test	
			t	*P*-value
MCA before				
Mean±SD	57.61±12.41	59.25±10.23	0.393	0.697
Range	38–76	47–80		
MCA during				
Mean±SD	65.30±14.61	65.50±11.90	0.040	0.968
Range	40–90	48–87		
MCA after				
Mean±SD	67.48±14.12	69.58±11.23	0.447	0.658
Range	42–94	55–92		
PCA before				
Mean±SD	63.65±12.08	69.17±13.89	1.218	0.232
Range	39–90	42–100		
PCA during				
Mean±SD	70.35±14.70	74.08±14.73	0.713	0.481
Range	42–112	50–112		
PCA after				
Mean±SD	72.04±11.18	82.0±11.66	2.465	0.019*
Range	46–98	66–110		

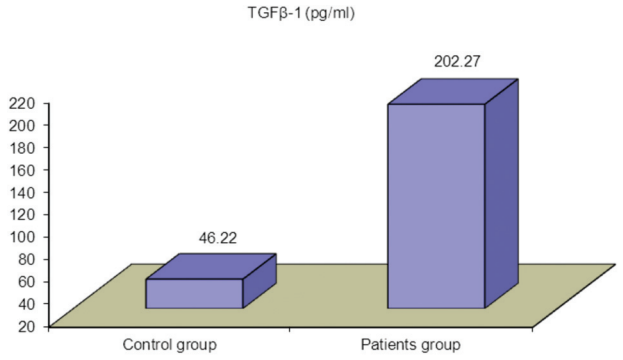
MCA, middle cerebral artery; PCA, posterior cerebral artery; PSV, peak systolic volume. *Means statistically significant.

Table 5 Comparison between patients' subgroups regarding peak systolic volume changes (difference before flash and after flash stimulation)

	Without aura (*n*=23)	With aura (*n*=12)	Mann–Whitney test	
			Z	*P*-value
PSV changes in MCA				
Median (IQR)	9 (7–12)	9.5 (8–12.5)	–0.805	0.421
Range	4–19	6–16		
PSV changes in PCA				
Median (IQR)	7 (5–9)	11 (9.5–14)	2.848	0.004*
Range	4–18	8–16		

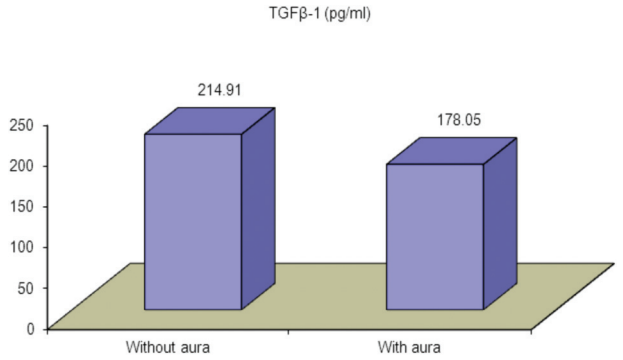
IQR, interquartile range; MCA, middle cerebral artery; PCA, posterior cerebral artery; PSV, peak systolic volume. *Means statistically significant.

Figure 1



Comparison between patient and control as regard serum levels of TGFβ-1.

Figure 2



Comparison between patient subgroups (migraine with aura and without aura) as regard TGFβ-1.

Table 6 Correlation between transforming growth factor β-1 and clinical data in patient group

	Transforming growth factor β-1 (pg/ml)	
	R	*P*-value
Duration of headache	0.348*	0.041*
Frequency of headache per month	0.708**	0.005*

*Means statistically significant. **Means highly significant.

vascular control, rather than in the primary vessel diameter changes [11]. The published results of TCD studies of the main cerebral arteries, performed in patients with idiopathic headaches, especially with migraine, are controversial [11]. Some authors could not find any changes, whereas the others observed increased blood flow [13]. In this study, we evaluated PSV of MCA and PCA as a parameter to assess cerebral vasoreactivity changes by using flash stimulation during the interictal migraine. We found that there is no significant difference between patients and control regarding PSV of MCA at baseline and during flash stimulation. However, after the end of stimulation, there was significant increase in PSV of MCA in migraineurs in comparison with normal participants. These results were in agreement with the study done by Bäcker *et al.* [11], the first TCD study done to show habituation. They used the flickering photic stimulation on all the migraineurs, both classic and common, and demonstrated that there were no significant differences of CBFV changes of MCA at baseline and during photic stimulation between patients and control. However, at the end of stimulation, the migraineurs show a steady increase in CBFV in MCA in comparison with normal participants who show a habituation [11].

In the present study, we found that PSV of MCA showed no significant difference between two patient subgroups (migraine with aura and migraine without aura).

This finding was in agreement with the study of Thie *et al.* [14], which measured mean flow velocity in MCA during motor tasks and found that there was no significant difference in cerebral flow velocity between migraine with aura and migraine without aura.

However, this study was contradictory to the study of Thomsen *et al.* [15] who examined MCA reactivity during hypocapnia and found higher reactivity index in migraine with aura than without aura.

Abnormalities of cerebrovascular reactivity in anterior circulation might be harder to detect, because the MCA supplies a much larger territory than the PCA. Focal increase of flow velocities in a small supply area during a specific cognitive task might, thus, not result in marked changes of blood flow velocities in the MCA stem, even if the MCA territory was involved in the migraine process [16].

Data suggested an altered neurovascular coupling in occipital cortex of patients with migraine interictally [11].

In the present study, we found that PSV of PCA at baseline, during flash stimulation, and after flash stimulation showed significantly higher values in patient group than control group. Moreover, the change of PSV at the end of stimulation from the baseline was significantly greater in the migraine group as compared with control group. These results are in agreement in part with the work done by Bäcker *et al.* [11] who used flickering photic stimulation to detect CBFV of PCA and demonstrated that regarding PCA, compared with normal participants, migraineurs showed significantly stronger CBFV changes at the beginning and after the end of stimulation; however,

during stimulation, no significant difference could be detected. Moreover, in 2004, Nedeltchev *et al.* [17] conducted a study using the checkerboard to stimulate the visual pathway and simultaneously recorded the MCA and the PCA. They concluded that CBFV increase in PCA and in MCA during visual stimulation was significantly larger and steeper in migraineurs than in controls (i.e. loss of habituation in migraineurs) [17].

The results are in agreement with the study of Sedighi *et al.* [12], who concluded that the change of PSV of PCA at the end of stimulation from baseline was significantly greater in the migraine group.

In the present study, we found that PSV levels of PCA after flash stimulation, and PSV changes, were significantly higher in migraine with aura. These results are in agreement with the study done by Wolf *et al.* [18], which found that visual evoked flow rate of PCA in patients with migraine with aura is significantly higher than in patients with migraine without aura.

In summary, we found altered cerebral vasomotor reactivity in the interictal phase in migraineurs, being more pronounced in migraine with aura.

In the present study, we evaluate the level of TGFβ-1 as an inflammatory marker for detection of inflammatory changes associated with migraine. We found a statistically significant increase in the serum levels of TGFβ-1 in patients with migraine in comparison with controls, and these levels had significant positive correlation with duration of headache and frequency of headache attacks per month. This is in agreement with the results by Ischizaki *et al.* [19] and Tietjan *et al.* [20], who studied premenopausal females during interictal period of migraine, and Güzel *et al.* [21], who found that the serum level of TGFβ-1 was significantly higher in migraineurs than in control group. These results were augmented by the study of Tietjen *et al.* [20] who found that there is a statistically significant positive correlation between TGFβ-1 and frequency of headache.

Regarding the two types of migraine, in the present study, we found that serum level of TGFβ-1 was significantly higher in patients with migraine without aura than in migraine with aura.

These results were not in consistent with the work of Ishizaki *et al.* [19], which detect TGFβ-1 in platelet-poor plasma in both types of migraine, and there was no statistically significant difference between migraine with aura and migraine without aura.

Moreover, these results were contradictory with the study of Güzel *et al.* [21], who demonstrated high statistically significant increase of serum TGFβ-1 in patients with migraine with aura than in patients with migraine without aura, which suggests that serum TGFβ-1 may be related to aura symptoms.

This contrast might be because of small sample size or decreased number of patients with migraine with aura.

Conclusion

This study indicates that vascular changes and neurogenic inflammation have a role in the pathophysiology of migraine. Vascular changes estimated by TCD were more pronounced in migraine with aura, whereas neurogenic inflammation, detected by evaluation of the level of TGFβ-1, was more pronounced in migraine without aura.

Functional TCD is a reliable and interesting method for the diagnostic evaluation and management of migraineurs. In addition, monitoring of the cerebrovascular response in migraineurs under prophylactic treatment might provide insight into the mode of action of the respective treatment modality.

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Conflicts of interest

There are no conflicts of interest.

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