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AUTONOMIC FUNCTION TEST IN MIGRAINEUR WITH PATENT FORAMEN OVALE

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ABSTRACT

Background: Several studies have reported a significantly higher incidence of patent foramen ovale (PFO) in patients with migraine with aura. Furthermore; several publications reported a consistent improvement of migraine symptoms following PFO closure. Some authors have emphasized a high concentration of vasoactive agents shunted to left circulation by PFO will trigger migraine attacks. The shunting of vasoactive agents to the left circulation eventually has its influence on autonomic function. **Aim**: Study the autonomic changes in migraineur during ictal phase to verify whether PFO triggering migraine attacks. **Methods:** The study included 112 patients, satisfying the International Headache Society criteria-2 for primary episodic migraine, within age group of 20 to 40 years of either sex. All patients underwent transthoracic Echocardiography. The autonomic function test (Expiratory-inspiratory (E: I ratio), Standing to Lying Ratio (S/L Ratio), 30: 15 ratio, Valsalva ratio and hand Grip Test) was performed in the neurology department under standardized laboratory conditions. **Results:** From 112 migraine patients, 34 (30.4%) patients having PFO (MPFO) and 78 (69.6%) not having PFO (MN). Megrainers with aura were 28/112 (25%), MPFO having aura 18/34 (52.9%) Vs. 10/78 (12.8%) MN patients, aura is significantly higher in MPFO P value <0.05. The mean values for E: I ratio, S/L Ratio, 30: 15 ratio, Valsalva ratio and hand Grip Test diastolic blood pressure are 1.17, 1.18, 1.19 , 1.32 , 9.4 mmHg respectively in MPFO compared to 1.43, 1.35 , 1.23, 1.41, 15.8 mmHg in MN respectively. All previous tests are significantly impaired in MPFO P value < 0.05. The study showed that patients with

MPFO had significant higher association with aura and markedly impaired AFT during the ictal stage compared to MN. **Conclusion**: Patients with MPFO have more aura incidence and markedly deranged autonomic function; accordingly we can suggest that PFO is a trigger factor for migraine or making migrainers more vulnerable to external triggers and results seem to suggest that PFO and aura have causal relation rather than comorbid association. The results affirm the role of PFO in the pathophysiology of migraine trigger.

KEYWORDS: PFO, migraine, aura, autonomic changes.

INTRODUCTION

Migraine is primary, chronic-intermittent neurovascular headache disorder characterized by episodic severe headache accompanied by autonomic nervous system dysfunction and in some patients, transient neurologic symptoms known as migraine aura.[1, 2] It's the second most common cause of headache, the lifetime prevalence of migraine ranges from 11% in males to 20% in females, with a mean of 16%.[3]

The pathophysiological mechanisms of migraine are complex and not fully understood. Both, genetic and environmental factors appear to play an important role in migraine etiology. Genetic effects, including autosomal dominant inheritance with incomplete penetrance [4] and coinheritance have also been reported.[5] The prevailing hypothesis regarding the pathogenesis of migraine is an inherited excitability of certain brain networks that, when triggered by particular endogenous or exogenous factors, leads to a cascade of events that result in headache, in addition to a multitude of other symptoms.[6]

The brain of the migraineur is particularly sensitive to environmental and sensory stimuli; migraine prone patients do not habituate easily to sensory stimuli. This sensitivity is amplified in females during the menstrual cycle. Headache can be initiated or amplified by various triggers.[7]

Following a number of publications reported a consistent improvement of migraine symptoms following patent foramen ovale (PFO) closure in patients who had suffered a stroke.[8-13]

Several studies have reported a significantly higher incidence of right-to-left shunt (RLS) and PFO in patients with migraine with aura than in patients with migraine without aura and control subjects.[10,14,17] At present, it is not clear whether this association is incidental or a

causal relationship. Although some authors have emphasized its role in the pathophysiology of aura,[15] PFO does not seem to affect the clinical manifestations of migraine with aura[18] and the extent of RLS fails to correlate with the severity of the clinical picture of the disorder[19], several recent studies link the presence of a RLS by PFO as a trigger of migraine attacks.[4, 6, 13, 18, 20]

The prevalence of PFO by autopsy studies in general population about 15–35%,[21-23] and appears to decrease with age.[21] Transesophageal echocardiography studies were report the prevalence of 24%, which is similar to autopsy studies.[24] Recent studies have noted that Transthoracic echocardiography (TEE) have similar accuracy in the detection of right-to-left atrial shunt [25-27] and it is accepted that (when image quality is good) TTE can be effective in the detection of PFO.[28, 29] PFO is more common in migraineurs with aura than in the general population and it is found in approximately 40% to 60% of people who have migraine with aura as compared to 20% to 30% of people in the general population.[5,12,18,21]

Although migraine without aura has been studied less extensively, it does not seem to be associated with an increase in the prevalence of PFO.[14] However, it is unclear if there is a causal relationship or simply a co-existence of these two conditions. PFO accounts for 95% of all right-to-left shunts.[30] It can be hypothesized that passage of blood directly from the right to left atrium, bypassing the normal filtering activity of the lungs, allows for paradoxical emboli and/or higher concentrations of vasoactive agents such as atrial natriuretic peptide, platelet factors, amines, serotonin, nitric oxide, kinins or other migraine precipitating chemicals to reach the brain and trigger migraine attacks.[12] Serotonin is normally metabolized by the pulmonary monoamine oxidase enzyme. Serotonin is released from aggregating platelets. Platelet activation and aggregation has been shown to be increased in patients with migraine.[31] In the presence of a PFO, serotonin is shunted away from the lungs and is postulated to trigger migraine.[32]

Another postulated mechanism in the presence of a PFO that predispose to migraine is hypoxia or thrombosis which promoting subclinical ischemia and paradoxical embolism.[33-35] The transient hypoxemia due to shunting of blood through the PFO causes microinfarcts in the brain, leading to irritation and a tendency for migraine.[32, 36] Resting and stress hypoxemia related to left-to-right shunting across a PFO has been demonstrated in the absence of pulmonary embolism.[37]

In 1930 Harold Wolf reported on the autonomic nervous system involvement in migraine headache.[38] Autonomic symptoms can occur during the pain phase[39,40] as different types of autonomic dysregulation[41, 42], or during normal daily activity between the attacks in which patient may have sympathetic instability and parasympathetic hypofunction.[43,44]

If right-to-left shunts have a role in triggering migraine attacks.[12] The shunting of vasoactive agents to the left circulation eventually has its influence on autonomic function. Accordingly we intend to study the autonomic function in migraineur at ictal stage to determine whether PFO is migraine trigger factor.

Patient and method

The study was conducted in the Department of neurology in Al-Diwanyah teaching hospital in association with the Department of medicine, between October 2013 and April 2015 The study include patients satisfying the International Headache Society criteria-2 for primary episodic migraine attending outpatient neurology clinic, home agreed to participate in the study, of either sex within age group of 20 to 40 years. The patients with neurological disorders, comorbid chronic physical illness: hypertension, arrhythmia, coronary artery disease, diabetes mellitus, uremia, features of polyneuropathy, infectious disease, any recent stressor, already taking drugs such as antihypertensives, triptans, ergots and oral contraceptives female at menstrual period were excluded from the study.

All participants underwent transthoracic Echocardiography performed using the Vivid 7 system (General Electric, Milwaukee, Wisconsin, USA) fitted with a 4.3 MHz multi-frequency probe with harmonic imaging. The apical 4-chamber view was used to optimize visualization of the atria, ventricles and interatrial septum. Patients had a suboptimal acoustic window or suboptimal quality of the images was excluded from the study, 112 eligible patients 42 male (37.5%) and 70 female (62.5%) were examined in the neurology department under similar laboratory conditions. The procedures were explained to them before actual assessment. All the measurements were performed in an isolated quiet air-conditioned room, and conducted during the morning hours, in a single meeting. Autonomic function tested (AFT) by ECG recording from standard leads using the student physiograph machine (INCO), while the blood pressure was measured under standard procedure by mercury sphygmomanometer with the Korotkoff's sound technique[45, 46], according to the American Heart Association Recommendations for Blood Pressure Measurement.[47]

Expiratory-inspiratory (E: I ratio): The test is performed in supine position. It's started with a rest period that gives patient time to relax then asked to breathe 6 breaths per minute. ECG record one minute baseline before proceeding to the deep breathing test. E: I ratio is the longest RR interval during expiration / shortest RR interval during inspiration from 5 cycles.

Standing to Lying Ratio (S/L Ratio): In this test each subject asked to stand quietly and then lie down without any support while a continuous ECG was recorded from 20 beats before to 60 beats after lying down. S/L Ratio is Longest R-R interval during 5 beats before lying down / Shortest R-R interval during 10 beats after lying down.

30: 15 ratio: After laid quietly for 3 minutes, each patient stood up and remained motionless with a continuous ECG was recorded. 30:15 ratio is R-R interval at beat 30 after standing /R-R interval at beat 15 after standing.

Valsalva ratio: After two deep expirations, the patients were made to blowing against closed glottis through a mouth piece attached to aneroid manometer and maintained a pressure of 40 mm of Hg for 15 seconds. A continuous ECG was recorded 1 minute before (resting period), during 15 seconds and 1 minute subsequent to strain period. Valslavas ratio is maximum R-R interval after the strain / shortest R-R interval during the strain.

Hand Grip Test: The patients were asked to apply sustained pressure on a standardized hand grip, at 30% maximum voluntary contraction for one minute, before and during one minute blood pressure was observed. The difference of diastolic blood pressure before and during the maneuver was calculated.

Data are presented as mean ± standard deviation (SD). Student t-tests were performed to indicate significant differences ($P < 0.05$). SPSS for Windows version 10.0 for the statistical analysis was used.

RESULTS

From 112 migraine patients, 34 (30.4%) migraineur havingpatent foramen ovale(MPFO) and 78 (69.6%)migraineur not havingpatent foramen ovale(MN).The mean resting systolic and diastolic blood pressure was 112.4 ±.3.4, 81.5 ± 3.2 mmHg respectively for MPFO where in MN it was 110.1±3.1, 84.2 ± 4.1 mmHg respectively. No statistical significant difference was found for both P values > 0.05.

The mean resting pulse rate for MPFO and MN were 77.9 ±5 and.6 82.5 ±6.1 respectively. We could not find any statistical significance for these result P value > 0.05. Megrainers with aura were 28/112 (25%), MPFO having aura 18/34 (52.9%) Vs. 10/78 (12.8%) MN patients, aura is significantly higher in MPFO P value <0.05.

Table (1): Mean values of autonomic function test, regarding migraineur not having patent foramen ovale and migraineur having patent foramen ovale.

AFT	MPFO	MN	P value
E: I	1.17	1.43	<0.05
S/L	1.18	1.35	<0.05
30/15	1.19	1.23	<0.05
Valsalva ratio	1.32	1.41	<0.05
HG/DBP rise	9.4 mmHg	15.8 mmHg	<0.05

MPFO- migraineur having patent foramen ovale,MN-Migraineur not having patent foramen ovale.

Table (2): Meanresting Blood Pressure and Pulse rate in bothmigraineurwith patent foramen ovalecompared tomigraineurwithout patent foramen ovale.

Parameter	Migraine with PFO	Migraine without PFO	P
Mean Systolic BP	112.4±3.4	110±3.1	>0.05
Mean diastolic BP	81.5±3.2	84.2±4.1	>0.05
Mean Pulse rate	77.9±5	82.5±6.1	>0.05

Table (3): Association between aura and patent foramen ovalein migraine patients

	Migraine with PFO		Migraine without PFO		
	N	%	N	%	P
Aura	18	52.9	10	12.8	<0.05
No aura	16	47.1	68	87.2	
Total	34	100.0	78	100.0	

DISCUSSION

The study showed that patients with MPFO had significant higher association with aura and markedly impaired AFT including; E: I, S/L, 30:15, Valsalva ratio and HG/DBP rise during the ictal stage compared to MN.MPFO have higher association with aura agreed with previous studies [10, 15-17] that show more incidence of PFO in migrainers with aura. Furthermore, subjects with atypical features of aura had 4-fold greater odds of having a PFO compared with patients with typical aura[48, 49] Even, if we agreed that PFO and migraine could be co-inherited disease with a comorbid association[4], our results seem to suggest that PFO and aura have causal relation rather than comorbid association.

There were no significance difference regarding the mean resting blood pressure and Pulse rate in both migraineur with patent foramen ovaleand migraineur without patent foramen ovale, that's prove the standards of laboratory conditions of the study and the similarity of both groups at resting conditions.

The AFT are significantly impaired in MPFO compared to MN, consequently; the PFO is seemed to be implicated in autonomic derangements in these patients. Our result is consistent with the findings of greater autonomic impairment in migraineurs with aura than without aura[50] The alteration in autonomic nervous activity in MPFO can be explained either direct of shunted vasoactive chemicals or PFO influences on autonomic response to pain.[51, 52]

Consequently, we can speculate the role of PFO in the pathophysiology of migraine trigger. This is supported by significant improvement of migraine symptoms following PFO closure.[9-14] And the higher incidence of migraine attacks in patients with RLS.[53] With the evidence of association between atypical migraine aura and RLS that seems to influence significantly the ischemic stroke risk independently of cardiovascular risk factors.[48]

A higher frequency of migraine attacks in patients with CHD without an intracardiacshunt, suggests additional mechanisms to explain the significant association of PFO with Migraine.[54]

CONCLUSION

Our study find that patients with MPFO have more aura incidence and markedly deranged autonomic function; accordingly we can suggest that PFO is a trigger factor for migraine or making migrainers more vulnerable to external triggers.

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