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RESEARCH ARTICLE

ROLE OF TRANSCRANIAL DOPPLER IN DETECTING RIGHT TO LEFT CIRCULATORY SHUNTS IN MIGRAINE HEADACHE PATIENTS.

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Abstract

Background: Migraine is a common disabling primary headache with an estimated prevalence of 13% of the general population. Right to left circulatory shunts, mostly patent foramen ovale, and migraine especially migraine with aura do exist. There is a debate whether this is a mere coincidence or a causal relationship. Objective: We aimed to evaluate the relationship between right to left circulatory shunt and migraine using transcranial doppler.
Methods: Using ultrasound studies (transthoracic echocardiography, transesophageal echocardiography, and transcranial color-coded duplex of middle cerebral artery) for detection of circulatory shunts in migraine patients either migraine with or without aura. Results: there is statistically significant presence of right to left circulatory shunts in the group of migraine with aura, in which 46.7% of the group showed latent shunts and were detected by transcranial doppler (p value = 0.006). While only 13.3% of the common migraine group had right to left circulatory shunt (p value =0.54).
Conclusion: Right to left circulatory shunts detected by TCD is a significant finding in migraine with aura. They are mostly latent shunts that are not present under basal conditions. They don't cause hemodynamic abnormality in resting conditions. TCD is a good ultrasound diagnostic tool for detecting right to left circulatory shunts.

Introduction:-

Migraine is a very common condition worldwide. Estimates of its prevalence have varied widely, ranging from 3% to about 22%. (1) A reasonable estimate of one-year prevalence of migraine in adults is 10 to 12% (6% in men and 15-18% in women). (2) Migraine is classified according to the ICHD-II into migraine without aura, migraine with aura (either typical aura with migraine headache, typical aura with non-migraine typical aura without headache, familial hemiplegic migraine, sporadic hemiplegic migraine, basilar type migraine), childhood periodic syndromes, retinal migraine. (3)

Many theories were suggested to explain migraine pathophysiology. One of these theories is the old vascular theory in which intracranial vasospasm of the cerebral arteries causes the aura of migraine, and then extracranial vasodilatation. (4) Another theory is the cortical spreading depression in which there is marked, enduring reduction of

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electrical activity that spreads out from that location in all directions, involving successively more and more distant parts of the cerebral cortex.[5] Many studies explained the role of chemical neurotransmitters in trigeminovascular system including serotonin and calcitonin gene related peptide.[6] The recent theory adopts the neurovascular theory with neural centers as generator of the migraine.[7]

A right-to-left shunt is defined as a cardiac shunt that allows deoxygenated blood to flow from the right heart to the left heart. The shunt may occur at different levels, either intra-cardiac, para-cardiac, related great vessel and intra-pulmonary shunts. They can be related to a congenital lesion or post-surgical sequelae. [8] Patent foramen ovale (PFO) is a common normal finding in infants but often closes in the early years. Estimates of the incidence of patency of the foramen ovale in adults at autopsy range from 9 to 35%. Persistence of patency of the foramen ovale usually is discovered as an incidental finding during echocardiography, or during the work up of cryptogenic stroke. [9] Patent foramen ovale is not a hole in the heart, it takes place when there is failure of fusion of overlapping flaps of the septum premium and septum secundum in fetal life, causing a less than 5-mm, slit-like valvular opening in the interatrial septum. [10]

PFO are usually diagnosed incidentally with the aid of echocardiography. The gold standard for the diagnosis is the transesophageal echocardiography (TEE) which gives a clearer picture than the transthoracic echocardiography (TTE) which may miss cases of PFO, with or without shunting, as it is mainly operator dependent and needs experience for its discovery.[11] Transcranial Doppler (TCD) was introduced to detect shunting from right to left side of the heart and it has the privilege of being noninvasive and can be done at bed side without specific preparation.[12] It has more concordance rate with the TEE in detection of right to left shunt than the transthoracic echo, but it lacks the ability to localize the shunt which may be intra or extracardiac. Another advantage of the transcranial duplex is the ability to perform the Valsalva maneuver which may be difficult in transesophageal echocardiography. [13] [14]

Patients with ASD had a 1.8- to 3.6-fold higher prevalence of migraine (24.2%; 95% CI, 16.7 - 33.7%) than the 9.4% found in the Japanese general population after adjusting for sex and age. [15] The underlying mechanism of the possible relationship between PFO and migraine remains speculative. It has been postulated that PFO may allow venous-circulating, migraine-triggering, vasoactive chemicals to bypass the pulmonary filter and reach the cerebral circulation to induce a migraine attack. [16]

Subjects and Methods: -

Subjects

The study was carried out at Neuropsychiatry Department, Center of the Neurology, Psychiatry and Neurosurgery (CNPN), and Cardiology Department from June 2017 to June 2018. Forty-five subjects were enrolled in the study and were subdivided into 3 groups: **Group (1):** included 15 subjects suffering migraine with aura. **Group (2):** included 15 subjects suffering migraine without aura. **Group (3):** included 15 healthy volunteers, age and sex matched. This group was considered as control group. The patients must fulfil the criteria of the ICHD-II, between the age of 15-45 years. We excluded patients with known rheumatic heart disease, and secondary headaches. Informed consent was obtained from all patients after explaining the nature of this study.

Methods

Complete history and clinical assessment:

Intensity of the headache was estimated by the Numeric Pain Rating Scale in which the patient is asked to make three pain ratings, corresponding to current, best and worst pain experienced over the past 24 hours. The average of the 3 ratings was used to represent the patient's level of pain over the previous 24 hours. [17]

Ultrasound studies:

Transcranial color-coded duplex ultrasonography of middle cerebral artery (TCCD):

The TCCD was performed using Philips HD11 XE device and S3-1 MH linear probe. The patients were in supine position with the arm horizontal. An intravenous Daflon catheter is inserted into the antecubital vein and is connected to a 250-ml bottle with physiological solution by means of a flexible tube to maintain venous access. Insonation of one middle cerebral artery (MCA) using TCD was performed. The entire circle of Willis was displayed with color power Doppler technology through temporal bone window. The sample volume was placed on the middle cerebral artery (MCA) at a depth of 50-55 mm and Doppler flow images were monitored simultaneously with color /power imaging duplex. The contrast agent is rapidly injected as a bolus with the patient at rest. In the event of little or no detection of micro embolic signals (MES) in the insonated MCA, the examination was repeated

using the Valsalva maneuver (VM). The contrast agent is injected 5 seconds prior to the start of the VM; the overall duration of the VM is 10 seconds. The patients started the VM on examiner's command. The strength of the VM can be controlled by peak velocity of the Doppler curve. The time when the first MES appears within the MCA was noted. The VM should be trained with the patient before the examination. The VM should not be performed, if the test has revealed a 'curtain pattern' at basal conditions. Otherwise, the possibility of air embolism during VM exists in principle. Position of the patient was changed in the case of a first negative test. [18] [19]

Contrast preparation
The amount of saline/air mixture should be 10 ml (1 ml air and 9ml saline). A three-way stopcock was connected to a 10-ml syringe I (containing 9 ml of 0.9% saline), a 10-ml syringe II (containing 1ml air aspired) and the antecubital vein of the patient. An 18-gauge intravenous catheter was used to increase sensitivity. One milliliter of air (syringe I) and 9ml of saline (syringe II) rapidly exchanged between the syringes at least ten times. Afterwards, the air/saline mixture was injected into the patient as a bolus. Time window for detection of micro embolic signal between the intravenous injection of the contrast agent and its appearance in the insonated MCA is 25 seconds. The time needed for the contrast agent to pass from the antecubital vein to the MCA is about 11 s for a passage through an intracardiac shunt and about 14 s for a passage through a pulmonary shunt. Shunts appearing only after Valsalva maneuver are termed latent shunts. [20]

A four-level categorization is accepted according to the number of MES in the TCD spectrum using unilateral MCA monitoring:

Table 1:-Grading of right to left shunt by TCD:-

	MES number
Grade 1	No MES
Grade 2	1-10
Grade 3	More than 10
Grade 4	More than 10 with curtain

Transthoracic echocardiography for right to left shunt detection:
All patients underwent transthoracic echocardiography with Vivid-7 ultrasound device and MS3 probe.

Transesophageal echocardiography for right to left shunt detection:
In suspected cases where the TCD detects a shunt with or without Valsalva maneuver transesophageal echocardiography was done.

Statistical analysis:-
Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation and chi-square test by SPSS V.16: the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chi-square and likelihood-ratio chi-square. Fisher's exact test and Yates' corrected chi-square are computed for 2x2 tables. Analysis of variance [ANOVA] tests: According to the computer program SPSS for Windows. ANOVA test was used for comparison among different times in the same group in quantitative data.

Results:-
This study included 45 patients. In migraine with aura group 10 were females (66.7%) versus 5 males (33.3%). In migraine without aura group 12 subjects were males (80%) versus 3 males (20%). Control group was chosen as age and sex matching subjects to the other groups with 9 (60%) females versus 6 males (40%). In migraine with aura group 7 patients out of 15 (46.7%) had right to left shunt by TCD. All the shunts were latent and happened only with Valsalva maneuver. Five shunts were mild and two were moderate. In the group of migraine without aura 2 patients (13.7%) had right to left shunts of mild grade. None of control group had right to left shunt. This was significant as p value is 0.048 (less than 0.05).

By using TTE, in migraine with aura group only 2 (13.7%) shunts were detected in comparison to 7 shunts by TCD. The 2 shunts were through a patent foramen ovale. PFO was present with no shunt across it in 3 cases (20%). In migraine without aura group no shunts or PFO were detected. In control group only one PFO without shunt were detected (6.66%). TEE showed that in the shunt positive patients by TCD in migraine with aura group only 2 had

right to left shunt through a PFO. The others had PFO without shunt (latent shunt). TEE results in shunt positive cases showed right to left shunt in both cases. In control group the positive case for PFO by TTE showed no shunt by TEE. All the shunts discovered were grade 1 by TEE. The presence of PFO was statistically significance in group of migraine with aura (p value=0.008). In migraine without aura the presence of right to left shunt was not significant (p value = 0.483). Right to left shunt wasn't correlated with either the intensity or the number of attacks/months. Correlation between grade of right to left shunt and intensity of headache was 0.075 which is weak positive correlation with p value = 0.634. Number of attacks/months also wasn't correlated with grade of right to left shunt. Correlation coefficient = -0.14 which is weak negative correlation and wasn't statistically significant with p value = 0.349.

Agreement between TCD & TEE was high in control group as shown by kappa value of 1 with p value < 0.01. In migraine with aura, TCD was more sensitive than TEE and there was no significant agreement between TCD and TEE. In migraine without aura TCD matched TEE with significant agreement indicated by p value < 0.01. TCD & TEE were more sensitive than TTE.

Table 2:-Demographic and clinical characteristics in migraine patients and control

		Migraine with aura (15)	Migraine without aura (15)	Control subjects (15)	P-value
Demographic characteristics					
Sex	**Male**	5 (33%)	3 (20%)	9 (60%)	0.89
	Female	10 (66.7%)	12 (80%)	6 (40%)	
Age		38.61 ± 6.47	37.82± 4.62	38.63± 5.36	0.625
Residency	**Urban**	9 (60%)	8 (53.3%)	5 (33.3%)	0.76
	Rural	6 (40%)	7 (46.7%)	10 (66.7%)	
Clinical characteristics					
Type of aura	**Visual**	15 (100%)			
	Sensory	0			
	Motor	0			
Type of visual aura	**Fortification**	11 (73.3%)			
	Scotoma	4 (26.7%)			
Intensity of headache	**Moderate**	11 (73.3%)	9 (60%)	-	0.35
	Severe	4 (26.7%)	6 (40%)		
Pattern of headache	**Episodic**	13 (86.7%)	12 (80%)	-	0.5
	Chronic	2 (13.3%)	3 (20%)		

Table 3:-Right to left shunt detected by sonographic studies

		Migraine with aura (15)	Migraine without aura (15)	Control subjects (15)	P-value
Transthoracic echocardiography (TTE)	**Shunt positive**	2 (13.7%)	0	0 (0%)	0.12
	PFO	5 (33.3%)	0	1 (6.7%)	0.018
Transesophageal echocardiography (TEE)	**Shunt positive**	2 (13.7%)	2 (13.7%)	0	0.334
	PFO	7 (46.7%)	2 (13.3%)	1 (6.7%)	0.019
Transcranial doppler (TCD)	**Shunt positive**	7 (46.7%)	2 (13.7%)	0 (0%)	0.003
	Shunt negative	8 (53.3%)	13 (86.7%)	15 (100%)	
Grading of shunt detected by TCD	**Mild**	5 (33.3%)	2 (13.3%)	0	0.048
	Moderate	2 (13.3%)	0	0	
	Severe	0	0	0	
Permanent vs latent shunt	**Permanent**	0	0	0	0.004
	Latent	7 (46.7%)	2 (13.7%)	0	

Table (4) Agreement between TCD and TEE shunts

	Migraine with aura	Migraine without aura	Control
TCD	7 (46.6%)	2 (13.3%)	0
TEE	2 (13.3%)	0	0
K	0.299	0.0	1
P-value	0.104	1	0.0

Discussion:-

The relationship between circulatory right to left shunt and migraine, especially migraine with aura has been a matter of controversy. The role of circulatory right to left shunt in migraine pathogenesis is not clear. Some studies concluded it is only an association. On the other side, some studies proposed an etiological role.

This study was designed as a case control study between 3 groups. Each group recruited 15 subjects. Group 1 included patients with migraine with aura. Group 2 included migraine without aura group. Group 3 included control subjects who were age and sex matched.

Regarding gender there was no statistical difference in gender among the three groups despite the fact that there was a female predominance. That was shown by a p value 0.89 (less than 0.05). The cause that subjects were chosen as sex matched. Female predominance reflects the fact of the increased prevalence of migraine in female population. These data are consistent with B. Lee Peterlin, et al (2011) in their study that evaluated sex and gender difference in migraine. [22]

When history was taken for aura it was always of visual type. That was statistically significance as p-value is (0.01) which is less than 0.05. This reflects the fact that visual aura is the most common type. [23] Visual aura may be positive (e.g. fortification spectrum) or negative (e.g. scotoma). Fortification spectrum was a significant type of visual aura as p value is (0.01) less than 0.05. This was not the case in other studies. **Queiroz, et al (2011)** reported that despite the fact that fortification spectra are the classic visual aura, the most common visual aura was blurred vision. The difference may be caused by not giving importance for blurry vision and make assumption that they are due to refractive errors. On the other hand, positive visual phenomena attract their attention more. [24]

Migraine is either moderate or severe. In migraine with aura group moderate headache percentage was (73.3%). Severe headache percentage was (26.7%). In migraine without aura group moderate headache had percentage of (60%). Severe headache had percentage of (40%). The difference was not statistically significant. In migraine with aura group episodic headache had percentage of (86.7%). The percentage in migraine without aura group was (80%). Chronic headache was present in a percentage of (13.3%) in migraine with aura group. The value was (20%) for migraine without aura. The difference between the 2 groups was not statistically significant.

After performing transcranial duplex the results of the current study showed a statistically significant presence of right to left shunt in the group of migraine with aura, 46.7% of the group showed latent shunts which were detected by transcranial Doppler (p value = 0.006) compared with only 13.3% of the common migraine with a shunt (p value =0.54) compared with 0% of the control group by TCD. This was consistent with the results of a recent study by Koppen Hille, et al (2012). [25]

On the other side this was not the case as Michael Küper, et al (2013) found that the difference between three groups on a population-based study to be non-significant. They used only TCD on MCA with agitated saline contrast but no other method. Even though right to left shunt was numerically higher, there was no statistical difference. Their values were: migraineurs with aura (45.2%) compared to migraineurs without aura (34.1%) and controls (41.5%). [26]

All the shunts detected by TCD were of latent type appearing only after Valsalva maneuver. Strong significance for the presence of latent shunts more than permanent shunts in migraine headache. This is indicated by a p value of (0.004) less than 0.05. In Michael Küper, et al (2013) study permanent shunts as opposed to latent shunts were more

frequent in patients with migraine with aura 40.5%, migraine without aura 23.3%, controls 24.4%. Again, the higher number was not statistically significant as p value = 0.173. [26]

Despite the numerically less findings regarding shunts, PFOs were discovered by TTE in a way that is significant for migraine with aura. The difference for PFO more than shunt may be caused by the TTE being less sensitive than TCD. This was consistent with the results of TJ Schwedt, et al (2008) who found a low-to-moderate grade of evidence from observational studies supporting an apparent association between PFO and migraine. [27]

On the contrary Pallav Garg, et al (2010) found no association between migraine headaches and the presence of PFO in this large case control study. They recruited 288 patients with the control group age and sex matched. They used TCD and TTE, both with agitated saline enhancement. [28]

Patent foramen ovale was detected more frequently than right to left shunt by TEE. This may be due the difficulty to perform Valsalva maneuver in TEE. There was a significant association between PFO and migraine headache more for migraine with aura as indicated by a p value (0.019) less than 0.05. The same study of Takaya et al (2016) found that 30% of patients with ASD experience migraine with. [29] TTE was the least sensitive with 2 right to left shunts in migraine with aura group (13.3%). No shunts were detected in the migraine without aura group or the control group. Only PFO was discovered without shunt in the 2 groups 2 in migraine without aura and one in control group.

Agreement between TCD, TTE & TEE was high in control group as shown by kappa value of 1 with p value < 0.01. In migraine with aura TCD was more sensitive than both. There was no significant agreement between TCD and TEE. In migraine without aura TCD matched TEE with significant agreement. A study comparing the two methods by Ana Iglesias Mohedano, et al (2014) found that concordance of 76.9% was found between TCD and TEE, but in 6 cases the shunt wasn't detected by TEE. This outcome may be related with the better effectiveness of the Valsalva maneuver with TCD than with TEE.[30] Another study evaluating the three methods by Teresa González-Alujasa, et al (2011) concluded that TTE and TCD showed higher sensitivity (100% vs. 97%; no significant difference) than TEE in the diagnosis of PFO (86%; P < .001).[31] Our findings are going with Mojadidi et al (2014) who found that TCD is a reliable, noninvasive test with excellent diagnostic accuracies, making it a proficient test for detecting RLS. TCD can be used as a part of the stroke workup and for patients being considered for PFO closure. If knowledge of the precise anatomy is required, then TEE can be obtained before scheduling a patient for transcatheter PFO closure. [32]

Conclusion:-

Right to left shunt by TCD is a significant finding in migraine with aura. This is met by a similar significance of PFO detected by TEE. The same significance was not noted in migraine without aura. Right to left shunt in migraine patients are mostly latent shunts that are not present under basal conditions. They don't cause hemodynamic abnormality in resting conditions.

TCD is more sensitive in detecting right to left shunt than TEE and TTE. This may be due to the ability to perform maneuvers that increase right atrium pressure like Valsalva maneuver with ease by TCD as it is noninvasive method. It is difficult to perform Valsalva maneuver in TEE. TCD lacks the ability to anatomically locate the shunt. It merely points to its presence and can only define it as cardiac or extracardiac. Anatomical localization is better done by TEE.

Ethics approval and consent to participate

The study was approved by the ethical committee of the department of Neuropsychiatry, Faculty of Medicine, Tanta University. All subjects provided informed consent to participate in the study.

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