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High prevalence of patent foramen ovale in migraine with aura

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Abstract In this study we evaluated the presence of patent foramen ovale (PFO) in a cohort of 25 consecutive patients suffering from migraine with aura (MA) during an attack presenting to the emergency ward of an Italian hospital. Patients underwent brain magnetic resonance imaging (MRI) with contrast medium, routine coagulation tests, contrast transcranial echocolour-coded sonography (c-TCCS) and transoesophageal echocardiography (TEE). Of the enrolled patients, 88.7% showed a PFO according to the c-TCCS test, whereas only in 72% TEE confirmed the presence of PFO. This discordance could be due to the fact that c-TCCS is more sensitive even with shunts with minimal capacity also located in the pulmonary vasculature. After surgical treatment of the PFO, MA disappeared within two months. Also, the treatment with warfarin as well as with acetylsalicylic acid and flunarizine was able to dramatically reduce the frequency of migraine attacks. These data indicate

a higher prevalence of PFO in MA vs. normal population (OR=2.92) and could suggest that the presence of arteriovenous (AV) shunts could represent a trigger for MA attacks as well as for stroke, but more studies are needed to confirm this preliminary hypothesis.

Key words Aura • Migraine • Patent foramen ovale

Introduction

The patent foramen ovale (PFO) is a residue of foetal circulation and is found to be patent in approximately 20%–30% of the adult population. In these subjects there is an interatrial right-to-left (R-L) shunting when right atrial

pressure exceeds the pressure present in the left atrium. The association between PFO and stroke and other neurological diseases has been well documented by both prospective and historical studies [1, 2].

Transoesophageal sonography represents the gold standard for the diagnosis and follow-up of patients suffering from neurological diseases possibly due to

embolisms from a PFO. This technique can also detect the morphological features of the shunts, and this is significant because the amplitude of the shunt is related to the embolic entities [3]. Conversely, contrast transcranial Doppler (c-TCD) is the most sensitive method to detect R-L shunts, the majority of which are due to PFO [4, 5].

A possible relationship between migraine with aura (MA) and paradoxical embolism caused by PFO has been reported. A high prevalence of MA is reported in patients with paradoxical embolism, suggesting a possible role of this association in the occurrence of cerebrovascular events [6]. Right-to-left shunts are also associated with some forms of decompression illness, suggesting the possibility that these shunts have a role in the aetiology of MA [7]. These observations suggest that paradoxical gas embolism may precipitate MA.

Moreover, a closure of PFO in patients with transient cerebral ischaemia, suffering from MA, induced a dramatic improvement of MA episodes, suggesting that aura may be triggered by factors that reach the brain by escaping the lung's filter [8].

To investigate the prevalence of PFO in patients suffering from MA, we studied a cohort of 27 consecutive subjects referring to the Emergency Ward of the Reggio Emilia Hospital during MA attack.

Patients and methods

Patients

Twenty-seven consecutive patients with attacks of MA presenting to the Emergency Ward of the Santa Maria Nuova Hospital of Reggio Emilia, from April to August 2003, complained of having a MA. Two subjects who refused to undergo the transoesophageal echocardiography (TEE) were excluded from the study evaluation and only 25 subjects (17 women and 8 men) were enrolled. The diagnosis of MA fulfilled the ICHD-II criteria [9]. Patients attending this study were well aware of their MA and followed a number of prophylactic treatments including beta-blockers, flunarizine and amitriptyline, but never treated their attacks with acetylsalicylic acid (ASA). We performed the Italian version of the Migraine Disability Assessment Scale (MIDAS) for an overall evaluation. After the first visit, all the patients were given a diary chart to record the number, intensity and duration of the migraine attacks, and the drugs taken.

Study design

The patients underwent routine examinations in the Emergency and Neurology Wards, including brain magnetic resonance imaging (MRI) with contrast medium, c-TCCS and a TEE. Coagulation parameters and blood values were considered in all subjects.

MRI was carried out with a Philips 1-tesla (USA) apparatus. A positive result was obtained when morphological lesions in T2 record were found, possibly due to recent or past ischaemic lesions.

The c-TCCS was performed using a Philips-Sonos 5500 device (Andover, MA, USA), exploring the temporal window with mesoencephalic axial access monitoring the cerebral medium artery [10]. Before the test, both intracranial arteries speedy measurement and their anatomical aspects locking at arterial-vein malformations (MAV) or aneurysmatic malformations were performed. In this last case we performed the examination by using coronal access in the temporal window.

High-intensity transient signals (HITS) were counted for 25 s after the end of the Valsalva manoeuvre, and the numbers of HITS were classified in one of four categories (zero HITS, 1–10 HITS, >10 HITS without curtain, and curtain) following the Blersch method [4].

TEE was performed by using an echocardiograph device "Philips Sonos 5500" (Andover, MA, USA) equipped with a multi-frequency probe S3 and transoesophageal multi-polar probe. The presence of PFO was defined by a R-L shunt at rest or after a Valsalva procedure after a IV injection of solution of mixed saline 9 ml plus air 1 ml.

A bolus with this contrast medium was injected into a forearm vein both at rest and in the Valsalva condition. The passage of more than 3 microemboli in the following three cardiac cycles was considered a diagnosis for PFO. This procedure was repeated a maximum of four times [6].

Atrial septal aneurysm was defined as in literature [10]:

- Presence of septal bulging over 10 mm then theoretical septal plain.
- Basal extension over 15 mm.

The Valsalva manoeuvre was performed by deep breathing and followed this procedure, according to the international recommendations of the Consensus Conference [11]:

- Five seconds after injection of saline solution, the patient began Valsalva manoeuvre lasting for at least ten seconds.
- Test positivity was obtained by the reduction of at least one-third of the systolic flow velocity on the middle cerebral artery (MCA).

The Ethical Committee (EC) evaluation was unnecessary because the patients followed the routine diagnostic-therapeutic protocol established by the Emergency and Neurology Wards protocols, which have already been approved by the local EC. All the patients were informed about the diagnostic procedures and expressed an explicit consensus. Only two patients refused to perform the TEE, and therefore were not included in this study.

The prevalence of PFO in the normal population of Reggio Emilia was explored in a study performed on the general population by a sonology specialist at the end of 2000. The study proposed to evaluate the performances of the new Echodoppler apparatus and to define basic parameters: 44 healthy volunteers underwent TCCD with contrast medium following the international criteria as reported above. These subjects were 19 males and 27 females, mean age 38.4 years (range 24–56), without any pathological condition and not suffering from MA. In this group there were 14 positive cases (30.5%) for a R-L shunt, but only in 5 cases (10.8%) was the shunt large. The data were analysed using a SPSS package programme.

Results

Patients' demographic characteristics are reported in Table 1. The clinical characteristics of patients' migraine are reported in Table 2.

The MRI images were referred to the following cases: female, 46 years old, assuming oestrogenic treatment (OP) and suffering from MA since the age of 28 years with a prolonged TR signal (thyroid hormone receptor) in right caudate; female, 36 years old, non-smoker, no OP, MA since the age of 18 years, small TR lesion in the left occip-

ital area; female, 43 years old and male 47 years old, non-smokers, no OP, with diffuse small non-specific lesions.

We presumed cardiovascular risk factors for patients when one or more of the following were present: smoking more than 20 cigarettes/day, use of oestrogenic and blood hypertension.

All the enrolled patients underwent both transcranial and transoesophageal sonography and results are reported in Table 3. The presence of a number of HITS significant for arteriovenous (AV) shunts are shown and the concordance of the two analyses are listed in the last column.

Table 1 Characteristics of patients

Patients, <i>n</i>	Sex	Age, years \pm SD	Onset of aura, years \pm SD	Patients with vascular risk, <i>n</i>	Brain positive MRI, <i>n</i>
8	M	42.5 \pm 9.8	32.1 \pm 11.5	1	1
17	F	38.8 \pm 12.05	26.1 \pm 11.1	1	3
25	Total number	40.2 \pm 11.3	28.1 \pm 11.2	2	4

Table 2 Characteristics of patients at the enrolling time

Migraine index	Intensity	Aura, min	Aura type	MIDAS
0.03	2	20	Typical	2
0.008	3	35	Typical+sensorial	2
0.5	3	45	Typical	4
0.01	2	18	Typical	2
0.06	2	30	Typical	3
0.01	1	13	Typical+sensorial	3
0.03	2	30	Typical	3
0.28	3	20	Typical	4
0.03	3	60	Basilar-type	3
0.03	3	40	Typical+sensorial	2
0.06	2	25	Typical+sensorial	1
0.01	2	20	Typical	3
0.14	3	20	Typical+sensorial	3
0.1	2	10	Typical	2
0.28	2	10	Typical	2
0.006	3	40	Typical	2
0.005	3	30	Typical+sensorial	3
0.009	2	20	Typical	1
0.03	3	30	Typical+sensorial	2
0.03	2	13	Typical	2
0.1	2	30	Typical+sensorial	4
0.009	3	15	Typical	3
0.01	2	25	Typical+sensorial	4
0.02	3	40	Typical	2
0.001	3	30	Typical+sensorial	2
0.03	3	45	Typical	2
0.06	3	30	Typical	2
Mean 0.07	2.48	27.55		2.51
SD 0.11	0.58	12.11		0.84

Table 3 Results of sonography tests

	<i>n</i>	TCCS negative	TEE negative	TCCS positive	TEE positive	TEE/TCCS, %
Male	8	1	2	7	6	85.7
Female	17	2	5	15	12	80.0
All	25	3	7 (28%)	22 (88%)*	18 (72%)	81.8**
Control group	46		32 (69.5%)		14 (30.5%)	

*OR TCCS<->TEE=0.93

** c^2 test= p <0.001 (positive vs. negative)

Table 4 Patients' therapy and follow-up

ASA 300 mg	Warfarin	ASA 300 mg+flunarizine 5 mg	Surgery	4-month outcome
12				<50% of aura attacks
	2			No attacks
		6		<60% aura attacks
			5	No attacks

Doses are indicated as total daily amount

The types of aura reported by patients with PFO were: typical (13), with aphasia (3), basilar-type (1) and ictal (2). There was no relationship between the type of aura and the length of the disease and/or the entity of the PFO (ANOVA test). There was a strong relationship between TCCS and TEE positive tests. Only in one case was this referred to the first aura episode. This patient showed a large PFO and was surgically treated with complete remission. In five cases an atrial septal aneurysm was found, but there were no surgical indications and patients were treated with ASA.

The follow-up data of the patients are reported in Table 4.

Surgical closure of PFO was always decided after a cardiosurgery consultation. This procedure was selected taking into account the patient's age, the shape of PFO, the presence of aneurysm, the presence of ischaemic lesion showed by MRI and an overall evaluation of thrombosis risk.

All patients who underwent PFO closure were treated with ASA. Sporadic episodes of MA, and subsequently no other episodes of MA were recorded in five patients, treated surgically with devices implantation, during the first 6–8-week period. A six-month follow-up showed, only in one case, few migraine attacks and a new sonography examination with TEE was performed, showing a R-L

shunt probably due to an incomplete closure of the interatrium device.

The seven negative patients to the TEE test were treated with flunarizine 5 mg and ASA 300 mg (one patient) and with ASA 300 mg/day (six patients). The overall outcome (no. of attacks) at the 4-month follow-up was zero attacks for the first patient and 3 attacks for the other six cases.

Patients treated with surgical device showed clinical features that were comparable with other cases with respect to the frequency, intensity of migraine and to the aura type. The only difference was the *complete* response 6–8 weeks after the treatment. Considering the four-month follow-up period, we did not find significant differences between treatments, probably because of the small sample we examined.

Discussion

TCCS could be considered a safe and effective technique to detect R-L shunts. This method is characterised by the use of an intravenous infusion of air and saline, shaken as contrast medium that produces a suspension of micro-

emboli with a diameter inferior to red blood cells, but unable to pass through the lung filter. This medium injected into a forearm vein goes to the heart and, in case a R-L shunt is present, it can be detected by a TCCS in the arterial tree at the level of the MCA, suggesting a possible PFO or, more infrequent, other AV shunts [10].

The Valsalva manoeuvre enhances the sensitivity of the test and recent studies comparing the TCCS with the transoesophageal Doppler (TEE) indicate that the Valsalva manoeuvre shows a 100% sensitivity in TCCS vs. TEE and a specificity around 73% [10–13].

In this study we used the TCCS because this method can immediately exclude concomitant pathologies like AV congenital malformations, aneurysms and stenosis of intracranial arteries. Moreover, in these patients it could be relevant to study the functional densitometry with the wash in-and-out curves. In fact, the use of new contrast media allows the study of the secondary harmonic waves that are related to the parenchyma perfusion, leading to new and important information on cerebral functions. At the moment these methods are used only in the study of cerebral ischaemia to guide the fibrinolytic therapy and not in the study of MA.

Moreover, TCCS can suggest the dimension and function of the shunt depending on the number of HITS and curtains present. When the TCCS patterns show a number of 1–10 HITS, the diameter of the shunt could be considered slight; moderate in case of >10 HITS without curtain effect; and severe when there is a curtain effect. If HITS are present at rest or after Valsalva manoeuvre, the shunt could be considered permanent or intermittent after Valsalva manoeuvre [5, 9, 14, 15].

In this study we examined a cohort of patients with MA and found that TCCS was positive in about 88% of patients referring an attack of MA, and TEE was positive for PFO in 2/3 of the subjects. The concordance of these two methods was high and significant ($p < 0.001$, χ^2 test). The higher prevalence of PFO vs. normal population studies was calculated as an odds ratio (odds ratio: 0.1496 Wald 95% CI: 0.2224<O.R.<0.8542 inverse OR $p2 < -> p1$: 2.29 (~SE=0.79)), which showed a significant difference ($p < 0.02$).

Only in four cases did TEE not confirm the presence of a PFO. This discordance could be due to the fact that TCCS is more sensitive, even with shunts with minimal capacity. The high percent of PFO that we found could be related to the characteristics of the study cohort of MA patients attending an emergency ward, which could not be exactly representative of the whole population of migraine patients.

Another point that should be discussed is the possible existence of medium AV shunts at lung level that can allow the passage of air contrast and therefore the air can

be detected in the brain arteries with TEES and Valsalva manoeuvre.

The major aim of the study was to confirm the high prevalence of PFO in MA. It is possible that these two conditions share a common pathological pathway, but physiopathological mechanisms underlying this possibility need further studies. If the complete resolution of aura symptoms after surgical closure of PFO emerged in the short-term follow-up at 4 months, in the long-term the relationship between these two disorders may be strengthened, even if it is reasonable to think that other biochemical parameters are involved in the mechanism of MA.

The hypothesis that there is a disturbance of the blood perfusion and oxygen supply during an aura episode is reasonable. There are some reports that hypothesise microembolic phenomena during stroke [16, 17] and MA [18–20]. The presence of PFO or atrial septal aneurysm has been well studied in recurrent cerebrovascular events (MAS) and the association between PFO and transient global amnesia (TGA) suggested that intermittent microemboli in the late vertebrobasilar vessels territory underlie at least some TGA cases. The prevalence of atrial septal aneurysms is significantly higher in patients with MA compared with patients with migraine without aura and with control subjects [21]. In this case, a formation of clots near the aneurysmatic surface which is often riddled with microscopic holes, or paradoxical embolisation through a coexisting PFO, or atrial septal defects, or valve prolapse, or other cardiac abnormalities potentially responsible for embolism could be hypothesised.

Migraine with sensorial and/or visual aura is another paroxysmal disturbance where a sudden malfunction of discrete cortical areas fed by terminal branches of the basilar artery could trigger the attack. In our opinion the migrainous aura is a complex syndrome, not always repetitive and with different clinical patterns. These differences could be representative of a variety of pathogenetic mechanisms; the spreading depression hypothesis could be modified in the future by new neuroimaging techniques.

Conversely, at the moment, there are no evident markers in the selection of patients who should undergo TCCS examinations and there are no biochemical or clinical elements related to PFO presence or size. In fact, there was no relationship between the type or length of aura phenomena and the TCCS or TEE results.

Transcatheter closure of PFO with or without ASA seems to be a safe, effective, minimally invasive procedure that ensures high closure rate and avoids life-long anticoagulant administration. It also seems to be an interesting strategy to treat patients with recurrent episodes of MA, and mid-term follow-up results appear favourable to prevent recurrent thromboembolism [8].

The pharmacological treatment seems to be effective in the same manner even with low doses of ASA and with treatment with a calcium channel antagonist like flunarizine at a dose of 5 mg/day. It was really interesting to note that the anticoagulant therapy with warfarin was more effective than other treatments, confirming the importance of the role played by coagulation and/or microembolism in the pathogenesis of MA.

In conclusion, our opinion is that MA patients could be studied with a c-TCCS and in case of positive results should also subsequently undergo a brain MRI and a TEE before final diagnosis [19].

Therefore, our results are only preliminary and in concordance with the data obtained by Evans [20]. Further studies are needed to confirm these data and develop guidelines for the treatment of patients with MA.

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