

Giorgio Dalla Volta
Massimiliano Guindani
Paola Zavarise
Simona Griffini
Alessandro Pezzini
Alessandro Padovani

Prevalence of patent foramen ovale in a large series of patients with migraine with aura, migraine without aura and cluster headache, and relationship with clinical phenotype

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G. Dalla Volta (✉) • M. Guindani
P. Zavarise • S. Griffini
Neurologia, Istituto Clinico Città di Brescia,
Brescia, Italy
e-mail: dalla@numerica.it

A. Pezzini • A. Padovani
Clinica Neurologica,
Università degli Studi di Brescia,
Brescia, Italy

Abstract A relationship between migraine and patent foramen ovale (PFO) has been observed in relatively small series of patients so far. Furthermore, the exact mechanism underlying such an association remains unknown. In the present study we determined the prevalence of PFO by contrast-enhanced transcranial Doppler (TCD) in a group of 260 patients with migraine with aura (MA+), 74 patients with migraine without aura (MA-), and 38 patients with cluster headache (CH). One-hundred-sixty-one MA+subjects (61.9%), 12 MA-subjects (16.2%), and 14 CH-subjects (36.8%) were PFO-carriers. The

association was independent on the frequency of migraine attacks and complexity of aura. Finally, among the 15 patients who had a history of at least one migraine attack occurring during a Valsalva maneuver only one subject turned out to be PFO-carrier. Our findings confirm previous observations of a link between MA+, CH, and PFO. They also suggest that such an association is independent on migraine clinical phenotype and is probably unrelated to the pathogenic mechanism of paradoxical embolism.

Key words Patent foramen ovale • Migraine • Transcranial Doppler

Introduction

Over the last decade, independent reports have suggested the hypothesis of a potential association between patent foramen ovale (PFO) and migraine [1, 2]. Although the exact pathogenic mechanism linking this anatomical variant to disease occurrence remains elusive at present, data of literature indicate that the association may be stronger in the subgroup of patients with migraine with aura (MA+), than in those with migraine without aura (MA-). Recently, a similar association has been reported in a relatively small group of individuals with cluster headache (CH) [3], thus supporting the assumption that interatrial septal abnormal-

ities might be a predisposing condition for different disorders. In spite of the consistency of these findings, further studies including larger number of individuals are necessary to substantiate such a hypothesis. Furthermore, several questions remain to be addressed. In particular, whether the reported non-significant association between MA- and PFO is the consequence of an underpowered comparison and whether any phenotypic difference exists between migrainous patients with PFO and those without, is still debatable. Finally, based on the concept of paradoxical embolism as a link between PFO and cerebral ischaemia, the possibility that migraine occurrence in subjects with a PFO may be related to triggering conditions, such as a strenuous physical activity, has never been tested so far.

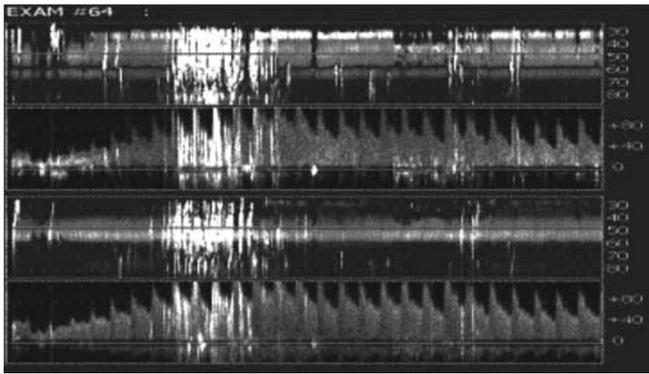


Fig. 1 Multiple embolic signals detected on middle cerebral artery

Materials and methods

The study group consisted of migrainous patients selected among those consecutively included in the database of the Headache Center – Istituto Clinico Città di Brescia, who were re-evaluated and underwent a PFO determination from January 2004 to December 2004. Patients fulfilling the International Headache Society diagnostic criteria [4] for MA–, MA+ and CH were considered. Only patients with moderate or severe headache intensity (Visual Analogical scale (VAS) ≥ 4) were included. For the purpose of the present study, the monthly frequency of migraine attacks in the subgroups of patients with MA– and MA+ as well as the complexity of aura in the subgroup of patients with MA+ were assessed in each patient and included in the analysis as phenotypic variables.

Finally, a further specific subgroup of migraine patients was selected based on the presumed triggering effect of strenuous physical exercise on headache occurrence. PFO was assessed in all

patients with TCD with IV injection of agitated saline. The technique consists of the injection of 20 ml of previously shaken saline as contrast-enhancing agent into a peripheral vein, while recording the flow velocity of the middle cerebral artery, insonated through the temporal window on the right side at a depth of 50–60 mm, with a hand-held probe. The appearance of transient spikes on the velocity spectral curve within 10 s of the intravenous injection of contrast medium is considered positive for interatrial right-to-left shunt (Fig. 1). The method has been previously validated in our institution and provides 90% sensitivity and 100% specificity, with an overall diagnostic accuracy of 95%, in comparison with transoesophageal echocardiography [5]. All contrast TCD were performed with a standard MultiDop (Esaote) device equipped with a 2-MHz transducer by two experienced examiners (MG, PZ) who were unaware of the status (MA+, MA– or CH) of the patients.

Results

The study group consisted of 372 patients (74 MA–; 260 MA+; 38 CH). PFO was detected in 161 subjects in the subgroup of patients with MA+ (61.9%), 12 subjects in the subgroup of patients with MA– (16.2%), and 14 subjects in the subgroup of patients with CH (36.8%). When phenotype variables (frequency of migraine attack and complexity of aura) were included in the analysis and their prevalence in each subgroup compared, no significant difference was found (Table 1). Finally, among the 15 patients who had a history of at least one migraine attack occurring during strenuous physical exercise (Valsalva manoeuvre) only one subject turned out to be a PFO-carrier.

Table 1 General characteristics, clinical presentation and prevalence of PFO in the study group

Characteristic	MA+ (n=260)	MA– (n=74)	CH (n=38)	MA+ PFO+ (n=161)	MA+ PFO– (n=99)	MA–PFO+ (n=12)	MA– PFO– (n=62)
Sex, male, <i>n</i> (%)	98 (37.7)	29 (39.2)	23 (60.5)	60 (37.2)	38 (33.3)	5 (41.6)	24 (38.7)
Age, mean (SD), years	32 (7)	35 (5)	43 (4)	31 (5)	33 (8)	34 (7)	36 (5)
Migraine attacks/mo, mean (SD)*	1 (2)	5 (3)		1 (2)	1 (2)	5 (4)	5 (3)
Migraine attacks days/mo, mean (SD)*	1 (2)	11 (2)		1 (2)	1 (2)	10 (3)	11 (2)
Migraine attack severity, %*							
Moderate	82	75		80	76	72	70
Severe	18	25		20	24	28	30
Aura, <i>n</i> (%)							
Visual disturbances	259 (99.6)			160 (99.3)	99 (100)		
Sensory disturbances	145 (55.7)			85 (57.9)	60 (60.6)		
Diphasic disturbances	46 (17.6)			30 (18.6)	16 (16.1)		
Typical aura without headache, <i>n</i> (%)	0 (0.0)			0 (0.0)	0 (0.0)		
Typical aura with non-migraine, <i>n</i> (%)	38 (14.6)			26 (16.1)	12 (12.1)		
Typical aura with migraine headache, <i>n</i> (%)	222 (85.4)			141 (87.5)	81 (81.1)		
PFO carriers, <i>n</i> (%)	161 (61.9)	12 (16.2)	14 (36.8)				

*In the last six months

Discussion

Our findings support the assumption of an association between PFO and MA+. In contrast, given the low prevalence of PFO among patients with MA-, the possibility that this interatrial abnormality may have a pathogenic role in such specific subgroup seems unlikely. Based on the results of the present study, the hypothesis of an influence of PFO on the pathogenesis of CH is also plausible. Our observation of a negative PFO-MA- association is apparently inconsistent with the results of recent observational studies in which a reduction of the frequency of migraine attacks was found after percutaneous closure of PFO in both the subgroups of patients with MA+ and MA- [6]. Although we cannot rule out the possibility of an underpowered analysis given the relatively small number of MA- patients in our group, it might be that the beneficial effect of PFO-closure on MA-

may be dependent on additional, and still unknown, co-existing factors, such as, for instance, the clinical presentation of disease. Although this is biologically plausible, stratification for the phenotypic subcategories we identified did not change our results. The same is true for the potential role of paradoxical embolism. As no interaction was observed among migraine occurrence, the triggering effect of Valsalva manoeuvre and PFO, we do not believe that such a mechanism may have any pathogenic influence. These findings prompt speculation that factors different from those predicted by phenotype might be operant in the complex relation between PFO and migraine. Overall, the exact pathogenic role of PFO in migrainous disorders remains debatable. On the basis of these observations, a therapeutical randomised case-control trial of percutaneous PFO closure in patients with different migraine subtypes has been designed and will be carried out in our institution.

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