Abstract In the last ten years a considerable bulk of evidence has accumulated on the relationship between migraine, particularly migraine with aura, and atrial septal defects, particularly patent foramen ovale (PFO). The increased frequency of PFO in migraine with aura, which almost parallels that found in stroke of unknown cause, the fact that in migraine patients PFO tends to be larger than in non-migraine controls and some positive results on migraine severity obtained after PFO closure have spurred speculation on a possible causal relationship. By applying the criteria proposed by Bradford-Hill to establish causality between associated phenomena, we try to demonstrate that PFO is not just a further example of migraine comorbidity but exerts a causal effect at least in the triggering of aura.

Keywords Migraine · Patent foramen ovale · Transcranial Doppler · Causation

Foramen ovale is an anatomical structure allowing physiologic right-to-left shunt (RLS) during foetal circulation. In over 70% of the general population, it comes to closure after birth. In the remaining 30% of cases, such communication is left “patent”, i.e., “open”, and represents a potential substrate for RLS during adult life [1]. Given its high prevalence in the general population, patent foramen ovale (PFO) cannot be considered a pathology itself. Nevertheless, a consistent body of epidemiological evidence has been suggesting a causal relationship between PFO and those strokes where an evident cause cannot be found, particularly in the young population [2]. In this subset of patients, a PFO is found in more than half of cases. Stroke clearly is a pathological condition and secondary prevention has to be pursued by every means, particularly in younger patients. So, there is little doubt that a PFO has to be searched for in young patients with a stroke of unknown origin [2]. But what about the PFO–migraine relation? Indeed, a PFO is as prevalent in migraineurs with aura as in stroke patients of less than 55 years [3, 4]. However, both migraine and PFO are common conditions and it is possible their association is no more than chance. Moreover, migraine is not commonly considered a threat as much as stroke is. Therefore, there is no current indication to screen migraineurs for a PFO. But if a causal link between migraine and PFO was demonstrated, would it change our way of looking at migraine?

In 1965, Sir Austin Bradford-Hill proposed, in a seminal paper [5], his well known criteria on the concept of causation: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy. Such criteria can be advocated to demonstrate that the PFO–migraine connection goes far beyond the simple association by chance of two common conditions.
Strength and consistency

The first two criteria of Bradford-Hill stipulate that to establish a causal relationship between two variables, their association must be strong and consistent across studies. Compared with non-migraineurs or migraineurs without aura, patients with migraine with aura have been invariably shown to have a RLS in about half the cases, with quite narrow confidence limits, the figures ranging from about 40% to about 60% [3, 4, 6–9]. It is perhaps worth noticing that the migraine–PFO association is of the same order of magnitude as that between stroke and hypertension or hypercholesterolaemia and far greater than that between stroke and diabetes [10].

Specificity

What is specifically associated with migraine with aura is not so much the PFO but rather the RLS caused by PFO, as is confirmed by the high prevalence of migraine found in RLS caused by other conditions such as pulmonary arteriovenous malformations (PAMVs). A number of studies demonstrated a significant association between migraine and hereditary haemorrhagic telangiectasia-associated PAMVs [11, 12]. The strongest case for specificity is given by the fact that the association is limited to migraine with aura and does not include migraine without aura or tension headache [4, 7, 9].

Temporality

Little is known on the genetic and biological bases of migraine, and it cannot be excluded that PFO and migraine could be manifestations of a common underlying condition, like endothelial dysfunction [13]. PFO is a physiological condition present well before birth and hence precedes any clinical migraine attack occurring during life.

Biological gradient

The rule of biological gradient implies that an increment in the load of the putative causative agent increases the likelihood of the appearance of the phenomenon under study. Schwerzmann and colleagues [15] have shown by means of transoesophageal echocardiography (TEE) that large shunts are nine times more frequent in migraine patients than in controls. By using transcranial Doppler, which allows a more quantitative measure of the amount of shunted blood delivered to the brain vessels, Anzola and colleagues were able to demonstrate, in a large cohort of more than 400 patients, that the shunt entity follows a gradient of increasing burden from controls to migraine without aura up to migraine with aura and that patients with both migraine and previous stroke have, on average, the largest shunt [16] (Table 1).

Table 1 Age and shunt degree according to cerebrovascular disease (CVD) and migraine condition

<table>
<thead>
<tr>
<th></th>
<th>No migraine</th>
<th>Migraine</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CVD–</td>
<td>CVD+</td>
</tr>
<tr>
<td>n</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>40/60</td>
<td>38/47</td>
</tr>
<tr>
<td>Age, mean±SD</td>
<td>48±17</td>
<td>55±14</td>
</tr>
<tr>
<td>Mean bubble count (SE)</td>
<td>38 (5)</td>
<td>55 (8)</td>
</tr>
</tbody>
</table>

Plausibility

It may therefore be plausible to hypothesise that: as PFO is associated with cryptogenic stroke [1, 2], and migraine increases the risk of stroke [16, 17], the underlying mechanism linking stroke and migraine is represented by the increased propensity of migraineurs to develop a paradoxical brain embolism because of a PFO. Wilmshurst and colleagues specifically addressed this issue in a recently published study that assessed the prevalence of clinically relevant atrial shunts in patients with past stroke, in patients with migraine, in patients with both conditions and in healthy controls [19]. The results showed, in line with the findings of Anzola et al., that patients with migraine and stroke had the highest likelihood of exhibiting a clinically relevant shunt, which led the Authors to conclude that “…the increased incidence of stroke in subjects with migraine compared with the general population is because they have a higher prevalence of large atrial shunts and hence an increased risk for paradoxical embolism” [18].

Experimental evidence

The evidence provided by studies reporting the effect of percutaneous PFO and PAVM [19] closure on migraine is quite consistent in suggesting a possible benefit. This applies not only to the oldest, retrospective studies [14, 20–27], but also to the only published prospective case-control study [28] and to the recently published prospec-