PATENT FORAMEN OVALE AND MIGRAINE: A REVIEW

Nikolaos Christos Xifaras
National and Kapodistrian University of Athens, Athens, Greece

Abstract
Introduction: Evidence exists in literature connecting a patent foramen ovale (PFO), a common cardiac septal defect, with migraine. Understanding the potential relationship between PFO and migraine could be crucial for developing effective management strategies. This narrative review aims to synthesize current evidence on the connection between PFO and migraine, exploring epidemiological data, pathophysiological mechanisms, and clinical and therapeutic implications.
Methods: A comprehensive literature search was conducted across multiple databases, including PubMed and Cochrane Library, for studies published up to May 2024, using specific keywords and inclusion/exclusion criteria.
Results: The prevalence of PFO is significantly higher in migraine patients, particularly those with migraine with aura (MA), compared to the general population. The pathophysiology behind this interaction is not yet clear; potential mechanisms linking PFO to migraine include right-to-left shunting, allowing microemboli or vasoactive substances to enter cerebral circulation, altered cerebral hemodynamics, and common genetic pathways. Clinical studies on the efficacy of PFO closure for migraine prevention have yielded mixed results, with MA patients often seeing a significant improvement of their symptoms.
Discussion: While a higher prevalence of PFO in migraine patients and plausible pathophysiological mechanisms support a potential link, the clinical benefits of PFO closure for migraine prevention remain inconclusive in non-aura migraine. Further research is needed to identify patient subgroups that may benefit from targeted interventions and to clarify the pathogenesis.

Keywords: headache, migraine, migraine with aura, patent foramen ovale, right-to-left shunt

ΑΝΟΙΚΤΟ ΩΟΕΙΔΕΣ ΤΡΗΜΑ ΚΑΙ ΗΜΙΚΡΑΝΙΑ: ΑΝΑΣΚΟΠΗΣΗ

Νικόλαος Χρήστος Ξιφαράς
Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών, Αθήνα, Ελλάδα.

Περίληψη
Εισαγωγή: Αρκετά δημοσιευμένα στοιχεία συνδέουν το ανοικτό ωοειδές τρήμα (PFO), μία συχνή ανωμαλία του μεσοκολπικού διαφράγματος, με την ημικρανία. Η κατανόηση μιας πιθανής σχέσης μεταξύ PFO και ημικρανίας θα μπορούσε να είναι σημαντική για την ανάπτυξη αποτελεσματικών θεραπευτικών στρατηγικών. Η παρούσα ανασκόπηση στοχεύει στη σύνθεση των τρεχόντων στοιχείων, διερευνώντας επιδημιολογικά δεδομένα, παθοφυσιολογικούς μηχανισμούς, και κλινικές και θεραπευτικές επιπτώσεις.
Μέθοδοι: Πραγματοποιήθηκε ολοκληρωμένη βιβλιογραφική αναζήτηση σε πολλαπλές βάσεις δεδομένων, συμπεριλαμβανομένων των PubMed και Cochrane Library, για μελέτες δημοσιευμένες έως τον Μάιο του 2024, χρησιμοποιώντας συγκεκριμένες λέξεις-κλειδιά και κριτήρια συμπερίληψης/αποκλεισμού.
Αποτελέσματα: Ο επιπολασμός του PFO είναι σημαντικά υψηλότερος σε ασθενείς με ημικρανία, ιδιαίτερα σε εκείνους με ημικρανία με αύρα (MA), σε σύγκριση με τον γενικό πληθυσμό. Όμως, η παθοφυσιολογία αυτής της αλληλεπίδρασης δεν είναι ακόμη σαφής. Πιθανοί μηχανισμοί περιλαμβάνουν την επικοινωνία από δεξιά προς τα αριστερά, επιτρέποντας σε μικροέμβολα ή αγγειοδραστικές ουσίες να εισέλθουν στην εγκεφαλική κυκλοφορία, την αλλοιωμένη αιμοδυναμική του εγκεφάλου, καθώς και κοινές γενετικές οδούς. Κλινικές μελέτες σχετικά με την αποτελεσματικότητα της σύγκλισης του PFO για πρόληψη της ημικρανίας είχαν μικτά αποτελέσματα, με τους ασθενείς με αύρα να βλέπουν συχνά σημαντική βελτίωση της νόσου τους.
Συζήτηση: Ενώ ο υψηλότερος επιπολασμός του PFO σε ασθενείς με ημικρανία και οι προτεινόμενοι παθοφυσιολογικοί μηχανισμοί υποστηρίζουν μια πιθανή σύνδεση, τα κλινικά οφέλη της επιδιόρθωσης του PFO για την πρόληψη της ημικρανίας παραμένουν ασαφή. Απαιτείται περαιτέρω έρευνα για τον εντοπισμό υποομάδων ασθενών που μπορούν να επωφεληθούν από στοχευμένες παρεμβάσεις και για την αποσαφήνιση του ρόλου του PFO στην οντότητα της ημικρανίας.

Λέξεις-κλειδιά: κεφαλαλγία, ημικρανία, ημικρανία με αύρα, ανοικτό ωοειδές τρήμα, δεξιά-προς-αριστερά διαφυγή

Introduction

Patent foramen ovale (PFO) is a congenital cardiac defect resulting from the incomplete closure of the foramen ovale, an opening in the septum between the right and left atria of the heart. This defect is present in approximately 25% of the general population, remaining asymptomatic in most individuals.[1] However, PFO has been implicated in various medical conditions, including cryptogenic stroke, decompression sickness, and, more controversially, migraine, particularly migraine with aura (MA).[2–4]

The potential link between PFO and migraine has garnered considerable interest in the medical community over the past few decades, which has led to the hypothesis that PFO may play a role in the pathophysiology of migraine through various mechanisms. With inconclusive or contradicting results in published literature, the clinical implications and even the nature of the link itself remain a topic of ongoing debate.[3,5-6]

This review aims to provide a comprehensive narrative of the current evidence on the relationship between PFO and migraine. By synthesizing findings from epidemiological studies, exploring proposed pathophysiological mechanisms, and evaluating clinical outcomes and therapeutic interventions, it seeks to clarify the potential role of PFO in migraine pathogenesis and inform clinical practice.

Methods

A comprehensive literature search was conducted to identify studies examining the relationship between PFO and migraine. The search was carried out in the PubMed, SCOPUS, and Cochrane Library databases, covering articles published up to May 2024. The following keywords and their combinations were used: "patent foramen ovale", "PFO", "headache", "migraine", "migraine with aura", "migraine without aura". Boolean operators (AND, OR) were utilized to refine the search results. Additional articles were identified through manual searches of reference lists from relevant studies and reviews.

Studies were included if they met the following criteria: (a) original research articles, review articles, or meta-analyses; (b) full-text publication in English; (c) investigated the prevalence, pathophysiology, or clinical implications of PFO in patients with migraine; and (d) involved human subjects. The exclusion criteria were as follows: (a) studies not available in full text; (b) non-peer-reviewed articles, conference abstracts, responses or letters; and (c) animal studies.

After data extraction, the narrative synthesis was organized thematically, focusing on several key areas, including the prevalence of PFO in migraine, the pathophysiology linking PFO and migraine, the clinical outcomes and potential benefits of PFO closure for migraine, and any current recommendations for managing patients with the two coexisting conditions.

As this review utilized previously published data, ethical approval was not required.

Results

Epidemiological data

The evidence of correlation between PFO and migraine has been at times inconclusive, with results both supporting and disproving any link.[6–9] However, systematic analysis of the literature has shifted the narrative in the last few years and the correlation has become more apparent.[4,10] According to these results, the prevalence of PFO in migraine without aura ranges from 11-34.1% and in MA from 14.6-77.9%.(3,5,11,12) In case-control studies this prevalence could be as high as 96% for MA, compared to a range of 16-25.7% in controls.[10] A systematic review by Schwedt et al. showed a higher prevalence of PFO in patients with migraine compared to the general population, and especially higher for MA (OR=2.54 and 3.21, respectively).[13] Observational data suggests that the prevalence of PFO does not differ significantly between episodic migraine and chronic migraine patients.[14]

As this link has been more highlighted, other factors have been identified as well, potentially leading us to better understand the pathophysiology behind it. A 2015 study has associated the degree of severity of PFO with the frequency of visual aura symptoms, although without a complete quantitative relation.[15] The impact of right-to-left shunt (RLS) in PFO is of particular interest. A higher prevalence of MA compared to a healthy control group was also identified in individuals with a high degree of RLS or with PFOs over 2.0mm (large PFO)[16] and RLS has also been connected to an earlier onset of MA.[17] RLS is thus possibly crucial in decrypting the mechanism (or mechanisms) connecting PFO and migraine, as we will examine below.

Despite the amounts of evidence in favor, larger population studies might be crucial to conclusively make a case for the degree of involvement of PFO in migraine, as the small patient groups examined in present case-control or observational studies lead many researchers to concerns of bias or low clinical significance.[6,13]

Pathophysiology

The pathophysiological processes that could be involved in this correlation are several and variable. One prevalent theory involves Cortical Spreading Depression, or CSD. CSD is a wave of transient neuronal and glial depolarization that spreads across the cortex and activates the trigeminal neurovascular

system. It is considered a major factor in the creation of migraine pain and has been particularly linked to the aura phase of migraine.[18] It is proposed that microemboli can pass through the PFO, bypassing the pulmonary circulation, and through their impact on the blood vessels of the brain, could trigger CSD through hypoperfusion or microinjuries, which is supported by the documented ability of focal ischemias to cause CSD.[19,20]

CSD can also be triggered through a low oxygen saturation in cerebral blood supply, which too can be caused by RLS, potentially giving us another clue about the aforementioned increase in prevalence and severity.[21] Another hypothesis involving the atrial shunt considers its impact on serotonin metabolism. Serotonin, which plays a significant role in migraines, is primarily produced by platelets peripherally, and PFO has been associated with increased serotonin production.[22,23] Peripheral serotonin normally gets inactivated in the lungs, but by not undergoing pulmonary filtration, the increased production and decreased inactivation could lead to changes in serotonin levels that can be linked to migraine attacks.[24] Sufficient evidence to support or disprove these theories does not exist at this moment.

Genetic factors could also be at play. One such factor could be found in the NOTCH receptor family, specifically the Notch3 gene. Notch3, a gene whose polymorphisms have been involved in CADASIL and MA, was shown to be associated with PFO closure in animal models.[25,26] However, neither this nor other genetic susceptibility theories have been confirmed and these hypotheses are not yet mature.[4]

Management

Although the therapeutic intervention most widely studied for migraineurs with PFO is closure of the septal defect, some evidence exists regarding pharmacological treatments. Potential medication regimens include antiplatelet agents like clopidogrel, as well as P2Y12 inhibitors such as ticagrelor.[27,28] In particular, research has identified that P2Y12 antagonists effectively inhibit the oxidative stress-induced platelet-associated tissue factor and reactive oxygen species expression, which are all implicated in the inflammatory and oxidative processes that trigger migraines.[29]

In general, the interpretation of clinical studies that have considered the efficacy of PFO closure for alleviation of migraine has yielded mixed results and has been the source of much of the controversy surrounding the subject. Three main RCTs have thus far evaluated the potential benefit for patients.[30-32] In all three RCTs, a large reduction in the frequency of migraine symptoms or a cessation of episodes was considered the primary endpoint of each trial. None of the trials reached their primary endpoint, although all noted a reduction in frequency.[30-32]

The MIST trial, conducted in 2008, identified no differences in migraine cessation after 6 months in patients who had received transcatheter PFO closure versus the control group, which was submitted to a sham procedure. The implant group did display a greater reduction overall headache days (P=0.027) and the importance of RLS in MA was again identified in the patient group.[30] A 2016 trial was prematurely ended due to enrollment issues, but analysis of the data post-hoc showed both a reduction in migraine with aura days and a higher percentage of total cessation of MA in the PFO closure group.[31] Finally, in the PREMIUM trial, the PFO closure group experienced a significantly greater reduction in migraine days compared to the control (P=0.025).[32]

Subsequent review of the data both from RCTs and other studies provides a comprehensive examination of the overall effects of repair, and the conclusions derived can provide a clearer picture. Four metanalyses have been conducted, combining a range of different studies. Their results generally show that PFO closure has resulted in significantly higher rates of migraine cessation, and significantly higher reduction in migraine days and migraine frequency in patients that underwent PFO closure.[33-36] Furthermore, with regards to changes on the impact of headache on daily life, closure has been associated with a significant decrease in patients' HIT-6 scores (SMD 1.23, 95% CI 0.52–1.95), although a similar finding was not discovered for MIDAS scores.[36] Despite the subjective nature of the HIT-6 score, data tend to support this observation, especially for patients with a larger pre-treatment RLS.[37,38]

Even though all metanalyses observed this benefit of treatment on headache duration and frequency, their interpretation of the overall indications in the data can vary, due in some part to the statistical differences between the MA patients and the greater migraine group or migraine without aura subgroup.[34] One study observed the reduction in migraine frequency was much more pronounced for MA compared to migraine without aura (P=0.03), which could again point to a separate causative pathway.[35] This concurred with results both from RCTs and from individual observational studies.[39] Extending those results, two more research teams concluded that PFO closure should be considered for treatment of MA, while refraining from supporting this for patients without aura.[34,35] The difference in response in MA patients is so great that it should possibly be considered a separate research entity.

While none of the previously published or analyzed studies dealt with pediatric patients, which should perhaps be considered a subgroup of their own, a recently-published retrospective analysis of 86

adolescents who underwent PFO closure as a treatment for migraine showed significant improvement in headache burden (83% with >50% reduction) or total cessation (54%).(40) In this patient population, too, patients with aura symptoms displayed greater improvement compared to patients without aura,[40] suggesting an age-agnostic mechanism.

Discussion

Even though the correlation of PFO and migraine has been controversial in literature, over the past years it has become more widely accepted that a link does exist.[6,8,33,36] Gradually, more supportive data are produced on the potential pathophysiological connections between migraine and an extant PFO. While the bypass of pulmonary circulation and filtration, with the subsequent action of microemboli and other vasoactive substances causing CSD, is the leading theory, other genetic or biochemical factors could be at play.[4]

Despite multiple studies synthesizing available data, the evidence on clinical benefits of closure for these patients is not yet concrete enough, at least not as an umbrella solution. Our limitations include the lack of large groups of patients, which preclude our ability to conduct better stratification analysis of the MA patient subgroup, which appears to be the one most benefiting from intervention.[6,34,36]

The results of this narrative review have their own limitations, which include the heterogeneity of the included studies in terms of design and outcome measures. Additionally, publication bias and language bias were considered as the search was limited to articles published in English. These factors were taken into account when interpreting the findings and drawing conclusions and should be kept in mind.

The current consensus does not propose that PFO closure should be performed explicitly for migraine prevention and treatment. It is unclear whether the most recently available results will create a demand for the reexamination of this statement; nevertheless, more data is needed for a comprehensive understanding of the complex situation, and especially research into clarifying the role of PFO in migraine pathogenesis as well as identifying patient subgroups that could benefit from targeted interventions may prove fruitful.

Conflict of Interest

The authors declare no conflict of interest.

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