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Editorial

Perinatal determinants of patent foramen ovale and neurological implications: towards biomarker-guided precision medicine

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"It is more important to know which kind of person suffers from a certain disease than knowing from which disease somebody suffers"
Hippocrates

Keywords

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Introduction

After birth, with the newborn's first breaths, profound changes occur in systemic circulation. Among the most significant are the increase in pulmonary blood flow and the functional closure of the foramen ovale. This is achieved through a decrease in pulmonary arteriolar resistance due to vasodilation induced by pulmonary expansion, and an increase in oxygen pressure with a reduction in CO_2. Added to this are the elastic forces of the rib cage, which lower pulmonary interstitial pressure, and the increase in venous return from the lungs, which raises left atrial pressure, reducing the pressure gradient between the two atria and thus promoting closure of the foramen ovale [1]. Once pulmonary flow has stabilized, constriction of the umbilical arteries reduces placental venous return to the right atrium, accentuating the pressure difference between the two atria and allowing the septum primum and septum secundum to approximate, thereby stopping interatrial flow. This closure in newborns is reversible during the first day of life and for several weeks is exclusively mechanical, because it depends only on the pressure difference between the two atria. Around 3 months after birth, however, the two septa typically fuse permanently, making closure of the foramen ovale physiological [2].

At the same time, systemic resistance exceeds pulmonary resistance and the flow through the ductus arteriosus reverses, establishing a left-to-right shunt that persists for the first 24-72 hours, until the ductus begins to close. The high partial pressure of oxygen and changes in prostaglandin metabolism cause vasoconstriction of the ductus arteriosus, leading to its definitive closure and the establishment of adult circulation, with the two ventricles pumping in series without any significant shunting. However, in the event of incomplete fusion between the septum primum and septum secundum and therefore in the presence of persistent communication between the atria, a patent foramen ovale (PFO) is observed, one of the most common variants of atrial septal defects (ASDs). Although this alteration shares the same anatomical and functional context as other ASDs, it differs from them in that it represents a functional defect of closure rather than a structural anatomical defect. Specifically, in approximately 70-75% of individuals, the fusion of the septa occurs within the first year of life, while in 20-30% a functional patency persists, maintained by increased left atrial pressure [3, 4]. Other possible causes may lead to failure of the PFO to close, including excessive resorption of the septum primum, leaving an insufficient valve, or poor growth of the septum secundum, which does not allow complete closure [5].

However, failure of the interatrial septa to fuse and persistence of PFO are not solely dependent on anatomical factors, but may reflect the impact of early environmental and biological conditions [4]. In this sense, the concept of perinatal programming provides an interpretative framework for understanding how fetal and neonatal adaptations can modulate not only cardiovascular function but also vulnerability to future neurological disorders. In this regard, there is growing clinical interest in the correlation between PFO and migraine with aura (MWA), given the detection of a higher prevalence of this defect in MWA patients. Nevertheless, only some patients benefit from closure [6]. This highlights the need for predictive biomarkers capable of selecting patients for minimally invasive treatment. Integrating such biomarkers with perinatal information could represent a decisive step towards precision medicine.

Perinatal programming role in patent foramen ovale persistence

In the 1980s, J.P. Barker first proposed the basis of perinatal programming. He observed that newborns with low birth weight had a higher risk of developing cardiovascular disease (including heart attack, hypertension) as adults, suggesting that intrauterine conditions in the early stages of life influence future health. This concept was initially defined as Fetal and Infant Origins of Adult Disease (FIOAD) and was later expanded into the concept of Developmental Origins of Health and Disease (DOHaD) [7, 8]. In fact, advances in scientific research have shown that, in addition to birth weight, there are numerous other prenatal and perinatal factors that influence future health, including maternal and fetal stress. DOHaD therefore presents itself as a broader theoretical framework, encompassing the entire intrauterine and perinatal environment with repercussions extending beyond the cardiovascular system to the metabolic, renal, neurological, immune and oncological domains [8]. In this context, failure of the PFO closure may be the result not only of an anatomical alteration but also of early environmental and biological conditions,

including prematurity, hypoxia and respiratory distress. Indeed, these conditions can critically interfere with the atrial pressure gradient and the fusion of the interatrial septa, thereby favouring persistence of the PFO [4]. Specifically, premature infants have been shown to exhibit particular haemodynamic fragility during transitional circulation, highlighting their greater likelihood of persistent patency of the PFO. Therefore, PFO can be considered a possible clinical marker of perinatal programming, reflecting incomplete adaptation to the critical processes of transition to extrauterine life [9].

Association of patent foramen ovale with migraine with aura

Numerous studies have highlighted PFO as a possible etiological factor in several clinically relevant syndromes, including MWA, which is the most frequently studied form in the context of PFO [3]. Migraine is a highly disabling primary headache disorder with high prevalence and significant personal and socio-economic impact. The Global Burden of Disease Study 2010 recognized it as the third most common disease worldwide [10] and, in the 2015 update, as the third leading cause of disability among individuals under 50 years [11]. The diagnosis is based on the ICHD-3 classification [12]; the main forms are migraine without aura (MwA) and MWA, characterized by transient, focal neurological symptoms that develop in 5-20 minutes and last up to an hour, predominantly of a visual nature [13, 14]. The first data supporting a relationship between PFO and MWA date back to 2 Italian studies [15, 16] in the late 1990s: Del Sette et al. [15] identified, using transcranial Doppler, a higher prevalence of right-to-left shunting in subjects with MWA; subsequently, Anzola et al. [16] confirmed these results, hypothesising a possible emboligenic role for PFO. Subsequent studies reported a prevalence of PFO among migraine sufferers ranging from 39.8% to 72%, with values of 40.9-72% in patients with MWA and 16.2-33.7% in patients with MwA, compared to an estimated overall prevalence of around 25%; compared to controls, individuals with migraine are approximately 2.5 times more likely to have a PFO [17]. Multiple pathophysiological mechanisms have been proposed to explain this association, including paradoxical microembolisms, which are able to bypass the pulmonary filter, reach the cerebral circulation and induce transient ischaemia with activation of cortical spreading depression, which is the basis of aura. In this context, platelet function abnormalities and an increased thromboembolic risk reinforce the role of PFO as a conduit for clots or platelet aggregates, which are also responsible for major ischaemic events [18, 19]. There is also the possible contribution of particular genetic and hemostatic alterations, such as protein C or S deficiency and resistance to activated protein C, observed more frequently in patients with MWA and stroke, suggesting a shared thrombophilic substrate [20-22]. Another mechanism is the possibility of the passage of vasoactive substances, such as serotonin and platelet mediators, which would normally be inactivated in the lungs, resulting in oxidative stress, endothelial dysfunction and platelet activation [23-26]. Other plausible hypotheses include autonomic dysfunction, with alterations in vasomotor control, sympathetic-parasympathetic balance [6, 27] and calcitonin gene-related peptide. This peptide is a mediator of the trigeminal-vascular system known for its ability to induce vasodilation and neuronal sensitisation during a migraine attack, but its role in patients with PFO and MWA is still undefined and remains under investigation as to whether its expression or activity can be modulated by the presence of the interatrial shunt [28].

Research into predictive biomarkers: the MANET project

The MANET project – an Italian study, funded by the European Union (NRRP-MAD-2022-12376277) – was launched to clarify the link between PFO and MWA, distinguishing between cases in which PFO acts as causal factor from those in which it is only an incidental finding. This distinction is crucial to provide a more targeted indication for closure, avoiding unnecessary interventions and optimizing clinical benefit. The study focuses on the identification of predictive biomarkers through a multidimensional approach that integrates platelet, haematological, endothelial and metabolomic data. The study is being conducted jointly by the Monzino Cardiology Centre (Milan), the IRCCS Policlinico San Donato (Milan), the Federico II University Hospital of Naples and the University of Cagliari, the latter playing a leading role in metabolomic characterization. The main areas of investigation include: analysis of platelet and microvesicular phenotypes as indicators of pro-

coagulant activation; evaluation of oxidative stress and redox alterations at the erythrocyte level; use of microfluidic models to simulate blood flow through the PFO and assess its haemorheological impact; study of endothelial function through endothelial colony-forming cells, to better characterize incidental cases; and integration of metabolomic profiles (plasma and urine) with clinical and biological data to construct a predictive model of benefits from PFO closure. The project, which began in 2022, involves the prospective enrolment of patients with MWA and PFO who are candidates for percutaneous closure, enrolled in the clinical centers set up by the project. Each patient is followed for 6 months, with pre- and post-closure assessments (T0, T1) including blood and urine samples. A group of healthy controls, matched for age and sex, serves as a comparator for biological analyses. The clinical impact of migraine is measured using the Headache Impact Test (HIT-6), a validated tool for assessing quality of life [29-31]. Thus, the MANET project stands out as a pioneering example of precision medicine. By combining metabolomic profiling of patients with MWA undergoing percutaneous PFO closure with integrated clinical and biological datasets, the project aims to build a composite biomarker model capable of guiding the selection of patients most likely to benefit from closure.

Conclusion

It is therefore possible to interpret PFO, long considered a benign anatomical variant, as a potential marker of vulnerability, resulting from interactions between perinatal programming, haemodynamic adaptations and predisposing neurobiological factors. The intrauterine and neonatal conditions that influence its closure therefore not only cause anatomical alterations, but may also reflect early imprinting processes capable of modulating cardiovascular and neurological trajectories later in life. Its correlation with MWA delineates a complex research field in which the causal relationship is not always straightforward and where the clinical benefit of closure remains limited to selected subgroups of patients. The identification of specific biological signatures is therefore an essential step in distinguishing cases in which PFO actively contributes to the pathogenesis of the disease from those in which its presence is merely incidental. One of the most promising tools is metabolomics, which provides a high-resolution snapshot of complex molecular profiles and integrates them with clinical and functional data. This "omic" approach paves the way for precision medicine capable of stratifying patients, tailoring therapeutic strategies and, potentially, preventing long-term consequences. Finally, multidisciplinary and multicenter research projects represent an ideal laboratory for this evolution, marking the transition from a vision focused exclusively on the morphology of the ASDs to a broader perspective, in which PFO is no longer just an anatomical anomaly but a marker of the complex interactions between perinatal development, cardiovascular physiology, and neurological function.

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Declaration of interest

The Authors declare that there is no conflict of interest.

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