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Case report

Migraine with aura after clopidogrel withdrawal: evidence of inflammation as a migraine trigger? – Case report

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Abstract

This article presents the case of a PFO (patent foramen ovale) closure patient with double antiplatelet therapy in whom aspirin was discontinued before clopidogrel and that, at clopidogrel withdrawal, presented "de novo" migraine with visual aura attacks. Migraines with aura associated with atrial right-to-left shunts (PFO and other atrial septal defects) are attributed to the arrival of vasoactive substances in the brain, since not cleared by the lungs. In this case, discontinuation of clopidogrel one year after PFO closure induced "de novo" migraine with aura. Rather than confirming the prophylactic effects of clopidogrel for migraine with aura, its triggering at clopidogrel withdrawal is more likely related to a proinflammatory effect of discontinuing clopidogrel. This proinflammatory effect has been described in cardiological research, and reinforces that patients receiving dual antiplatelet therapy (clopidogrel and aspirin) should always have clopidogrel discontinued before aspirin in order to avoid proinflammatory or pro-thrombotic events.

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Introduction

Clopidogrel is one of the most widely prescribed drugs in the world, accounting for several billion dollars of sales annually.[1] Besides its massive use in cardiology for primary and secondary prevention of ischemic heart disease, it has also been used for cerebrovascular disease primary and secondary prevention as well.[2] A less well-known feature of clopidogrel usage is that its discontinuation may trigger a pro-inflammatory and prothrombotic state, thus exposing its users to an unpredicted risk.[3,4]

Here we report a case in which discontinuation of clopidogrel used for primary stroke prevention in a patent foramen ovale (PFO) closure scenario prompted "de novo" migraine with aura headaches, suggesting that its withdrawal had triggered a pro-inflammatory state.

Case report

A 39-year-old woman with a history of migraine without aura and recurrent oral herpes presented with headache secondary to an acute episode of herpes virus type 1 meningitis, diagnosed by detection of lymphocytic pleocytosis and positive immunology. Further scintigraphy diagnosed concomitant aortitis. Her physical and neurological examinations were unremarkable. She was successfully treated with acyclovir, but at follow-up small white matter lesions were incidentally detected in an MRI of the head, prompting a diagnosis of PFO after neurovascular investigation. The PFO was occluded with an Amplatzer device and the patient was prescribed a daily dual antiplatelet regimen consisting of 100 mg aspirin and 75 mg clopidogrel. Aspirin was discontinued six months after PFO closure (confirmed by Transesophageal Doppler Sonography), and after an additional six months interval clopidogrel was suspended. Eleven days later, the patient started to experience recurrent episodes of "de novo" migraine with visual aura (fortification spectra) attacks. Clopidogrel was reintroduced and the migraines ceased. A new attempt to discontinue clopidogrel was associated with further episodes of migraine with aura, and both clopidogrel and aspirin were reinstituted for subsequent withdrawal, but this time clopidogrel was discontinued first. No episodes of migraine with aura occurred after delayed and stepwise discontinuation of both drugs.

Discussion

As said before, clopidogrel is world widely used for primary and secondary prevention of ischemic heart and cerebrovascular diseases, and one of these instances is in the setting of PFO closure.[1,2] Several studies have highlighted an association between migraine with aura and right-to-left atrial shunts such as PFO.[3,5-8] Studies have shown that 40–50% of patients who experience migraine with aura have PFO, significantly more than those experiencing migraine without aura and non-migraineurs (both 20–25%).[3] Observational studies suggest that transcatheter PFO closure in patients with paradoxical thromboembolism reduces the frequency and severity of migraine symptoms.[7] Clopidogrel inhibits platelet aggregation and may improve migraine induced or worsened by PFO closure.[6] Small non-randomized trials suggested a benefit when migraine was the primary indication for closure, but positive results were not found in the only randomized trial.[7,8] Adding clopidogrel to aspirin is associated with a marked reduction in platelet reactivity; this dual antiplatelet therapy offers significant clinical benefits.[9,10] Vasoactive substances can move from the circulatory system to the brain if they are not filtered by the lungs; this is the mechanism through which right-to-left atrial shunts are thought to trigger migraine with aura.[1-4] Occasionally, PFO closure with orthotic devices may induce or worsen previous migraines, usually within the first few weeks after the closure procedure. When used with aspirin to prevent primary and/or secondary cerebrovascular ischemia after PFO closure, clopidogrel has been found to prevent migraine with aura, probably because it inhibits platelet aggregation and associated release of serotonin.[5-7,11,12] Conversely, discontinuation of clopidogrel prescribed for cardiovascular ischemia has been reported to increase rates of ischemic heart disease and death, indicating to result in a pro-inflammatory state, whose pro-inflammatory markers were documented in other studies.[3,4] This feature of clopidogrel is seldom seen because it is usually the first drug to be discontinued in patients who receive combined antiplatelet therapy[8,9]

Unanswered questions about clopidogrel therapy remain, such as evidence of a "rebound" phenomenon at clopidogrel withdrawal secondary to both prothrombotic and/or pro-inflammatory effects. The occurrence of this "rebound" effect was suggested by increased platelet reactivity disclosed by thromboelastography (TEG) as the area under the response curve at 15 min measure (AUC15 TEG method) and increased pro-inflammatory marker soluble CD40 ligand (sCD40L) measured at its withdrawal.[10] This pro-inflammatory state would be responsible for the thrombotic adverse events and increased mortality mentioned above. Clopidogrel's antithrombotic effects are mediated via irreversible binding to platelet P2Y12 ADP

receptors, inhibiting ADP-induced platelet aggregation. At the same time, clopidogrel inhibits vascular inflammatory biomarker expression, thus producing an antiinflammatory effect.[3,4,6,7]

Unfortunately, inflammatory markers were not collected for this patient, but the lack of migraine with aura recurrence more than two years after clopidogrel's withdrawal suggests our hypothesis to be correct.

In spite of relying on a single case and assuming that a larger population based testing would be desirable, this case strongly suggests that migraine with aura can be triggered by platelet-related pro-inflammatory factors. This assumption does not exclude other mechanisms, since it reflects only a single aspect of very complex circuitry.

Bullet points

1) Discontinuation of clopidogrel one year after PFO closure induced "de novo" migraine with aura.
2) Clopidogrel discontinuation-related "de novo" migraine with aura probably results from a pro-inflammatory effect, a withdrawal phenomenon already described in cardiology research.

3) Patients receiving dual antiplatelet therapy (clopidogrel and aspirin) after PFO closure should always have clopidogrel discontinued before aspirin, in order to avoid pro-inflammatory or prothrombotic events.

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Conflicts of interest
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Ethical aspects
This work was in accordance with the principles of the Helsinki Convention and its subsequent amendments, as well as the Brazilian guidelines provided for in resolution 466/2012, with the data given in writing after approval.

Author's contribution
All authors had the same contribution

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