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Article *in* Neurology · May 2004
DOI: 10.2143/AC.63.5.2033223 · Source: PubMed

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Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine

Martijn C. Post, MD; Vincent Thijs, MD; Luc Herroelen, MD; and Werner I.H.L. Budts, MD, PhD

A patent foramen ovale (PFO) is one of the major causes of right-to-left shunt, and a causal relationship between migraine and a PFO has been suggested.[1] We evaluated whether percutaneous closure of a PFO was associated with changes in the prevalence of migraine.

Methods. Patient selection. Patients with a PFO who had a paradoxical embolic event or systemic desaturation and who underwent a percutaneous closure in our center between February 1999 and September 2002 were included. The medical files were reviewed. The ethical committee approved the study.

Evaluation of migraine. A questionnaire was composed in such a way that a neurologist could diagnose migraine with or without aura (MA+ and MA−) according to the criteria of the International Headache Society. The questionnaire was sent to all patients and focused on three periods: 1 year before and 2 months and at least 6 months after percutaneous closure. Two neurologists blinded to the patients' files diagnosed MA+ and MA−.

Statistical analysis. Within-patient comparisons of the absence or presence of migraine were performed with the McNemar's paired χ^2 test. Interobserver reliability was evaluated by measuring the kappa coefficient. p Value < 0.05 was considered significant. All statistical analyses were performed with GB Stat software (version 8.0; Dynamic Microsystems, Inc., Silver Spring, MD).

Results. Patient characteristics. Seventy-six patients (mean age, 50.7 ± 12.9 years) were selected, and 66 completed the questionnaire. In 57 patients, the period between PFO closure and completing the questionnaire was >6 months. The characteristics of patients who completed the questionnaire are summarized in the table.

Prevalence of migraine. The median time interval between the occurrence of a paradoxical embolic event and the closing procedure was 162 days (range, 0 to 3,613 days). The time between PFO closure and administration of the questionnaire was 579 days (range, 110 to 1,419 days).

Migraine was present in 26 of 66 patients (9 men and 17 women; 39.4%). Twelve (18.2%) had MA+, and 14 (21.2%) had MA−. Two months after closure, the prevalence of MA+ and MA− decreased to 6.1% (4/66) and 6.1% (4/66; $p < 0.05$ vs before closure). At 6 months or more, the overall prevalence of migraine was 15.8% (9/57; $p < 0.05$ vs before closure). The prevalences of MA+ and MA− were 5.3% (3/57; $p < 0.05$ vs before closure) and 10.5% (6/57; $p = 0.11$ vs before closure). The frequency of migraine attacks also decreased ($p < 0.05$). Seven patients were taking potential prophylactic migraine drugs 6 months after closure (six, β-blockers; one, calcium antagonists). The kappa coefficient for interobserver reliability for migraine was 0.8 ($p < 0.05$).

Discussion. Patients with migraine have a high prevalence of PFO.[2] An increased rate of MA+ among stroke patients with PFO was found compared with patients with PFO.[2] A causal relationship between PFO and migraine has been proposed. In individuals with a right-to-left shunt, a lower dose of venous trigger substances may be needed to induce migraine because the shunt permits the pulmonary filter to be bypassed.[1] Moreover, the prevalence of migraine seems to decrease subsequent to PFO closure in patients with decompression illness.[3]

We evaluated whether PFO closure in patients who mainly had cryptogenic stroke would be associated with changes in the prevalence of migraine. We found a high rate of migraine in patients with PFO (39.4%) and documented a significant and persistent decrease in prevalence of MA+ ≥6 months after PFO closure. The frequency of migraine attacks also decreased significantly. Our data might fit with the recently reported experience that MA+ decreased after PFO closure.[4]

Table *Characteristics of patients who completed the questionnaire*

	Migraine	No migraine	*p*
No. of patients (n)	26	40	
Age (y, mean ± SD)	55 ± 10	53 ± 12	0.48
Male/female	9/17	27/13	<0.05
Indication PFO closure			
Stroke (n)	24	37	0.94
Peripheral embolism (n)	2	1	0.33
Brain abscesses (n)	0	1	
Desaturation (n)	0	1	
Frequency of migraine attacks prior to closure			
Almost monthly (n)	9		
Almost weekly (n)	9		
Several times a week (n)	8		

PFO = patent foramen ovale.

The prevalence of migraine also decreases with age; however, we believe that the changes in our study are too pronounced to be explained by the natural history of migraine.[5] Most of our patients were treated with low-dose aspirin, which could also influence migraine prophylaxis. The effect of low-dose aspirin, if any, seems to be modest.[6] The placebo effect in migraine therapy is potent, but the decrease in prevalence of migraine in our study seems to be larger than reported placebo effect rates of 20 to 40%.[7]

Nevertheless, this study has important limitations. It is a retrospective, nonrandomized trial of patients selected from a hospital-based database. The questionnaire may be influenced by recall bias.

The prevalence of migraine in patients with a PFO is high. After ≥6 months, percutaneous PFO closure is associated with a decrease in the prevalence of MA+. Whether percutaneous PFO closure has the potential to manage migraine needs to be determined in a prospective randomized trial.

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Received September 15, 2003. Accepted in final form November 13, 2003.

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See also page 1399

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Prolactinoma presenting as painful postganglionic Horner syndrome

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Painful postganglionic Horner syndrome may be the initial presentation of an internal carotid artery (ICA) dissection and less frequently is a complication of cluster headache.[1] However, it is not a frequent presentation of pituitary adenoma. We describe a patient with prolactinoma that initially manifested with painful Horner syndrome and improved on dopaminergic therapy. Eighteen months after treatment was discontinued, the patient sought treatment for a cavernous sinus syndrome that responded well to high-dose dopaminergic therapy.

Case report. A 52-year-old man was examined by one of our staff neurologists for an intermittent right hemicrania, retro-orbital pain and a narrowed palpebral fissure in March 1999. He had no history of alcoholism, head trauma, hypertension, diabetes mellitus, chronic headaches, impotence, or decreased libido. He smokes one pack of cigarettes daily. Examination revealed a 2-mm ptosis of the right upper eyelid and a 2-mm pupil that failed to dilate in the dark and after hydroxyamphetamine. The left pupil, in contrast, measured 3 mm and dilated to 5 mm in the dark and to 8 mm after hydroxyamphetamine. Both pupils reacted to light and accommodation. Visual acuity (V_{ac}), color vision, visual fields, funduscopy, and remaining physical examination were normal. Brain MRI showed a discrete mass surrounding the carotid artery (figure, left). Serum prolactin level was elevated at 566.4 ng/mL (normal range 0.5 to 18.1 ng/mL). Bromocriptine 5 mg/d was initiated, and the patient experienced symptomatic improvement during the ensuing 6 months.

Thirty-two months later, he again sought treatment at our institution for worsening right-sided headache and diplopia. Eighteen months earlier, the patient decided to discontinue his bromocriptine. During the interval, he had no change in his history. Examination revealed a 4-prism diopter right exophoria and a partial right oculomotor nerve paresis with partial ptosis of the upper eyelid; symmetric limitation of infraduction, supraduction, and adduction; and a 4-mm pupil with preservation of pupillary responses. Additionally, there was complete right sixth nerve palsy with hypesthesia in the right V_1 and V_2 dermatomes. Color vision, funduscopy, visual fields, and V_{ac} were normal bilaterally. During the next 2 days, he developed a complete ophthalmoplegia of the right eye.

Brain MRI showed a 2.2 × 1.8 × 3-cm lesion filling the right cavernous sinus adjacent to, but not compressing, the optic chiasm (figure, middle). The tumor now encircled the cavernous portion of the right ICA. Serum prolactin at that time was 281.3 ng/mL. The patient was started on bromocriptine 15 mg daily and cabergoline 1 mg twice weekly. Ten days after cabergoline was added, serum prolactin level decreased to 22.1 ng/mL.

Four months later, follow-up MRI showed a 50% reduction in tumor bulk with the tumor still encircling the cavernous right ICA (figure, right). Clinically, he had resolution of the Horner syndrome and third and sixth nerve palsies, and return of facial sensation. In addition, there were no signs of aberrant regeneration. The patient was able to remain compliant with dual dopamine agonist therapy, except for nausea managed with ondansetron.

Discussion. A pituitary adenoma, presenting as a focal mass in the cavernous sinus, without diffuse sellar involvement, is distinctly uncommon. We are unaware of previous reports of pituitary tumors manifesting initially as postganglionic Horner syndrome. Although our patient did not have symptoms of hyperprolactinemia, a markedly increased prolactin level directed us to this diagnostic possibility. The successful effect of dopaminergic therapy, with resolution of the presenting symptoms and signs and virtual normalization of the serum prolactin level, left no doubt as to the diagnosis.

Prolactinoma is not initially thought of as a cause of an isolated involvement of postganglionic sympathetic fibers. Raeder[2] first reported simultaneous impairment of sympathetic and trigeminal nerve fibers in a patient with an extrinsic mass lateral to the cavernous sinus. Our patient mimicked this presentation with a mass intrinsic to the cavernous sinus. Unlike his case, there was no involvement of motor trigeminal fibers.

Our patient had already been treated successfully with a single dopamine agonist but now presented with cavernous sinus syndrome after discontinuing therapy for 18 months.[3] The main impetus to try simultaneous, high-dose dopamine agonists was to elicit a rapid response given the severity of the pain and ophthalmoplegia and to rule out the possibility of a prolactin-secreting carcinoma. The remarkable clinical and imaging response to dual dopamine agonists essentially served to elucidate the benign neuroendocrine character of the tumor, allowing a diagnosis without need for tissue biopsy or malignant tissue markers.[4]

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Received July 24, 2003. Accepted in final form September 8, 2003.

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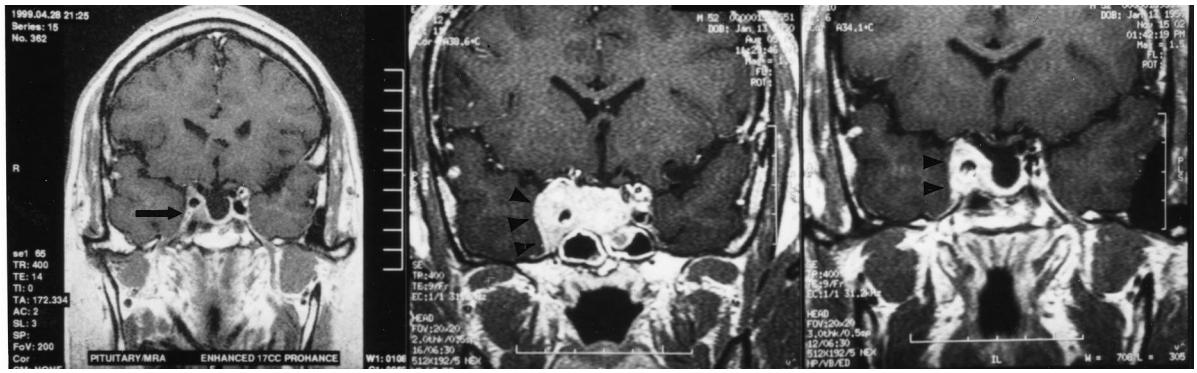

Figure. T1-weighted, contrast-enhanced MRI of brain. (Left) April 1999, performed after initial visit. (Middle) August 2002, ~1 month after starting dual agonist therapy. (Right) November 2002, only minimal symptoms present with reported 50% reduction radiographically in tumor bulk.