Improvement of Migraine After Patent Foramen Ovale Percutaneous Closure in Patients With Subclinical Brain Lesions

A Case-Control Study

Carlo Vigna, MD, FESC,* Nicola Marchese, MD,* Vincenzo Inchingolo, MD,† Giuseppe Maria Giannatempo, MD,‡ Michele Antonio Pacilli, MD,* Pietro Di Viesti, MD,† Matteo Impaglialetti, MD,⁎ Rosaria Natali, MD,§ Aldo Russo, MD,* Raffaele Fanelli, MD,* Francesco Loperfido, MD§

San Giovanni Rotondo and Rome, Italy

Objectives We sought to evaluate the benefits on frequency and severity of migraine recurrence after patent foramen ovale (PFO) closure in patients with subclinical brain lesions at magnetic resonance imaging (MRI).

Background Migraine improvement has been reported after PFO closure in patients with cerebrovascular symptomatic events. Subclinical brain MRI lesions are detectable in patients with PFO and in migraineurs.

Methods A total of 82 patients with moderate/severe migraine, PFO, large right-to-left shunt, and subclinical brain MRI lesions were prospectively examined for a 6-month period. Patients were subdivided into closure (n = 53) and control (n = 29) group according to their consent to undergo percutaneous PFO closure. In controls, therapy for migraine was optimized. Six-month frequency and severity of migraine recurrence were compared with baseline.

Results The number of total attacks decreased more in the closure group (32 ± 9 to 7 ± 7, p < 0.001) than in the control group (36 ± 13 to 30 ± 21, p = NS) (p < 0.001). A significant reduction in disabling attacks was observed only in the closure group (20 ± 12 to 2 ± 2, p < 0.001; controls: 15 ± 12 to 12 ± 12, p = NS). Migraine disappeared in 34% of the closure group patients and 7% of controls (p = 0.007); >50% reduction of attacks was reported by 87% and 21%, respectively (p < 0.001). Disabling attacks disappeared in 53% of closure group patients and 7% of controls (p < 0.001); >50% reduction occurred in 89% and 17%, respectively (p < 0.001).

Conclusions In migraineurs with a large PFO and subclinical brain MRI lesions, a significant reduction in frequency and severity of migraine recurrence can be obtained by PFO closure when compared with frequency and severity in controls. (J Am Coll Cardiol Intv 2009;2:107–13) © 2009 by the American College of Cardiology Foundation

From the Departments of *Cardiology, †Neurology, and ‡Radiology, Casa Sollievo della Sofferenza Hospital IRCCS, San Giovanni Rotondo, Italy; and the §Department of Cardiology, Catholic University Medical School, Rome, Italy.

Manuscript received September 29, 2008; accepted October 16, 2008.
Migraine, a form of headache affecting about 10% of the adult population (1), has been found to be associated with patent foramen ovale (PFO). In fact, migraineurs, and in particular those with aura, often show PFO (2,3); conversely, subjects with PFO more frequently complain of migraine than controls (2). In patients with cryptogenic stroke, percutaneous closure of PFO is a therapeutic option but has not been approved by the U.S. Food and Drug Administration pending results of randomized clinical trials. Moreover, in migraineurs with prior stroke, significant reduction or even disappearance of migraine attacks has been consistently reported as an additional benefit obtained by PFO closure (4–13). However, it has not been conclusively established if an invasive approach can improve symptoms also in “pure” migraineurs (i.e., patients without previous clinical cerebrovascular events).

Single or multiple brain lesions affecting the myelinated white matter are frequently observed at cerebral magnetic resonance imaging (MRI) in patients with both migraine and PFO and may represent silent ischemic events (14–16). The aim of the present prospective case-control study was to determine if percutaneous PFO closure, in comparison to standard medical therapy, may be beneficial for migraine in the selected subset of patients with large right-to-left shunt (RLS), subclinical brain MRI focal lesions, and moderate/severe migraine.

### Abbreviations and Acronyms

- **MES** = microembolic signals
- **MRI** = magnetic resonance imaging
- **PFO** = patent foramen ovale
- **RLS** = right-to-left shunt
- **TCCD** = transcranial color Doppler
- **VM** = Valsalva maneuver

### Methods

**Patients.** From June 2004 to October 2006, we prospectively examined 156 consecutive patients <60 years old with migraine and PFO, but without cardiac, aortic, or cerebrovascular causes for cerebral ischemia. Among this cohort, we selected the patients fulfilling the following criteria: 1) moderate/severe migraine (≥4 monthly attacks) with or without aura; 2) PFO with significant spontaneous or inducible large RLS as demonstrated by contrast transcranial color Doppler (TCCD); and 3) MRI evidence of single or multiple brain lesions. Patients with previous symptomatic episodes of cerebral ischemia (stroke or transient ischemic attack) were excluded. Other exclusion criteria were neurodegenerative, psychiatric, inflammatory, or infective diseases, pregnancy, contraindication to antiplatelet therapy, and chronic use of preventive medications against migraine.

The resulting group consisted of 82 patients (74 females, age 43 ± 10 years) that were clinically examined at our Cerebrovascular Disease Unit for a 6-month evaluation period. In all patients, clinical history was carefully collected, including cardiovascular risk factors and current medical treatment. Moreover, all patients had a complete laboratory screening for thrombophilia (antithrombin III, anticardiolipin, and antiphospholipid antibodies; lupus anticoagulant; levels of protein C and free protein S; homocysteine; and genetic tests for factor V Leiden and factor II). Thrombophilia was stated in the presence of abnormalities in ≥1 of these tests. This study received the approval by our Institutional Review Board Committee and all patients gave a written informed consent to participate.

**Assessment of migraine.** Migraine was evaluated by an experienced neurologist (V.I.), blinded to the protocol, in accordance with the International Headache Society criteria (17). Number and characteristics of migraine attacks were assessed during the 6-month evaluation period. Patients completed a detailed questionnaire where they reported frequency and severity of migraine. In particular, they indicated duration of attacks (time from onset until termination of an attack of headache, with or without symptomatic therapy), intensity of pain (according to a 4-point scale: 0 = no pain; 1 = mild pain, not interfering with usual activities; 2 = moderate pain, inhibiting but not completely preventing usual activities; 3 = severe pain, preventing all activities), occurrence of aura or accompanying symptoms (e.g., nausea, vomiting, photophobia, phonophobia), and response to symptomatic therapy.

We considered disabling the attacks with a duration greater than 6 h, associated with severe pain, not allowing any activity, with multiple accompanying symptoms and poor response to symptomatic pharmacological therapy (no change in the intensity scale).

**Transthoracic and transesophageal echocardiography, TCCD.** A transthoracic echocardiography was accomplished as a first-line examination. The diagnosis and subsequent anatomical and functional evaluation of PFO were performed by TCCD and transesophageal echocardiography with an ATL HDI 5000 system (ATL Ultrasound Inc., Bothell, Washington) at the time of recruitment. We achieved TCCD according to the recommendations of the Venice Consensus Conference (18). On the basis of microembolic signals (MES) count, we adopted a previously described 6-level scale for classification of shunt (19): 0 = absence of shunt (0 MES); 1 = latent shunt of mild degree (1 to 20 MES) after Valsalva maneuver (VM); 2 = latent shunt of moderate degree (>20 MES after VM, without curtain); 3 = latent shunt of high degree (curtain after VM); 4 = permanent shunt of mild/moderate degree (>10 MES at rest and curtain after VM); 5 = permanent shunt of high degree (curtain at rest).

All patients recruited had a large RLS (at least grade 3 at TCCD). Transesophageal echocardiography was performed with a 5-MHz phased multiplane probe. In addition to standard views, we studied the fossa ovalis region to detect...
a separation between septum primum and secundum. The criteria for atrial septal aneurysm were a diameter of the base ≥15 mm and a total excursion of the septum ≥10 mm (19,20). We qualitatively defined RLS at transesophageal echocardiography as the passage in left atrium of the same contrast agent used for TCCD studies (10 ml administered intravenously) within 3 cycles from the appearance in the right atrium at rest and, if negative, at the end of VM.

Brain MRI. We performed MRI using a 3-T system (GE Healthcare, Milwaukee, Wisconsin) according to an imaging protocol including: 1) a diffusion-weighted single-shot spin echo echo-planar sequence acquired in the anterior commissure–posterior commissure plane with 24 contiguous sections (diffusion gradient b values of 0 and 1,000 s/mm², repetition time: 6,000 ms, echo time: 120 ms, slice thickness: 6 mm with no gap, matrix of 128 × 128 pixels, and field of view of 240 mm); 2) fluid-attenuated inversion recovery (repetition time/echo time: 10,000/160 ms; inversion time: 2,200 ms); and 3) T₂-weighted turbo spin echo sequences (repetition time/echo time: 3,500/94 ms). For diffusion sequence, gradients were successively and separately applied in 6 orthogonal directions for a total acquisition time of 24 s. Trace images were then generated and apparent diffusion coefficient maps calculated with a dedicated software tool (Functool, GE Healthcare). The MRI studies were analyzed by 2 independent expert observers who were blinded to the clinical data. A consensus was achieved in case of disagreement. All patients enrolled had a MRI positive for white matter abnormalities defined according to other studies (14).

Subdivision of patients. At the end of the 6-month evaluation period, PFO closure was proposed for prevention of white matter lesions progression or thromboembolism. All patients were informed about clinical benefits and risks of PFO closure but not about possible effects on migraine. Fifty-three patients accepted to undergo the procedure (closure group), and 29 patients, who refused the PFO closure, constituted the control group. Medical therapy was re-evaluated in controls by a neurologist blinded to the protocol and, if necessary, a preventive drug for migraine was introduced, whereas patients in the closure group were allowed to take only symptomatic drugs during migraine attacks.

Percutaneous closure of PFO was performed under local anesthesia with intracardiac ultrasound guidance (9-MHz UltraICE, Boston Scientific Corporation, San Jose, California) to optimize the placement of the devices. The PFO occluder was Amplatzer in 35 (66%), fourth-generation Cardia in 10 (19%), and Cardioseal/STARflex in 8 (15%) patients. Afterward, patients received double antiplatelet therapy with aspirin (100 mg/day) and clopidogrel (75 mg/day) for 3 months and subsequently aspirin alone for 3 months.

Follow-up. Patients in the closure group underwent a complete transthoracic echocardiographic examination the day after the procedure and TCCD at 3, 6, 12 months and then every 12 months to evaluate a possible residual RLS. Moreover, transesophageal echocardiography was performed at 6 months. All patients were followed up for the occurrence of death, recurrent ischemic stroke, transient ischemic attack, or peripheral embolism. In the case of suspected recurrent cerebrovascular event, a new neurological examination, including brain MRI, was scheduled.

Follow-up of migraine started 6 months after the invasive procedure in the closure group and 6 months after optimization of therapy in controls. Frequency and severity of migraine were again assessed for 6 months, similarly as for the evaluation period. In comparison with baseline, >50% decrease in the number of total and disabling attacks was considered to be a significant clinical improvement for frequency and severity of migraine recurrence, respectively.

Data analysis. Data are reported as mean ± standard deviations. We used the Fisher exact test for categorical variables and the t test or Mann-Whitney U test for scale variables if data followed normal or non-normal distribution, respectively. Frequency of migraine at baseline and after treatment was compared by a Wilcoxon signed rank test. A propensity score, reflecting the probability to undergo percutaneous closure of PFO, was derived, including age, sex, presence of aura, septal aneurysm, thrombophilia, number of total and disabling attacks, and entity of RLS in the model. The goodness of fit was given by the area under receiver-operating characteristic curve being 0.89. The propensity score was incorporated into a logistic regression to adjust the estimate of the treatment effect on migraine. The level of significance for all tests was fixed at p < 0.05 (2-tailed). Statistical analysis was performed with Statistical Package for Social Sciences software (SPSS 11.0 for Windows, SPSS, Chicago, Illinois).

Results

Baseline characteristics and in-hospital post-procedural events. Patients in the closure group and controls did not differ significantly in baseline characteristics, including the prevalence of thrombogenic factors (Table 1). In the evaluation period, the total number of migraine attacks was similar in the 2 groups of patients (32 ± 9 vs. 36 ± 13, p = NS) but disabling attacks were more frequent in patients subsequently undergoing PFO closure (20 ± 12 vs. 15 ± 12, p = 0.012). We did not register any major acute clinical event (in-hospital deaths or systemic thromboembolic events) after PFO closure.

Follow-up. The mean duration of follow-up was 16 ± 7 months (range: 12 to 25 months), and no cardiovascular events occurred. At 3- and 6-month TCCD in the closure group, we found a residual grade 2 RLS in 1 patient and a
grade 1 RLS in 2 patients. These results were confirmed at 6-month transesophageal echocardiography and 1-year TCCD. Nine controls (31%) received preventive therapy for migraine after the evaluation period.

At 6-month follow-up, patients in both the closure and control groups reported a significant reduction in the number of migraine attacks (closure group: from 32/1100 to 7/1100, p = 0.001; controls: from 36/1100 to 30/1100, p = 0.038), but the reduction was greater in the first group (p = 0.001) (Fig. 1). Migraine completely disappeared in 34% of PFO closure patients and 7% of controls (p = 0.007) (Table 2). A significant improvement in frequency of migraine recurrence was registered in 87% and 21% of them, respectively (p = 0.001) (Table 2).

At 6-month follow-up, only patients in the closure group reported a significant decline in the number of disabling attacks (p = 0.001) (Fig. 1). Migraine completely disappeared in 34% of PFO closure patients and 7% of controls (p = 0.007) (Table 2). A significant improvement in frequency of migraine recurrence was registered in 87% and 21% of them, respectively (p = 0.001) (Table 2).

At 6-month follow-up, only patients in the closure group reported a significant decline in the number of disabling attacks (p = 0.001) (Fig. 1). Migraine completely disappeared in 34% of PFO closure patients and 7% of controls (p = 0.007) (Table 2). A significant improvement in frequency of migraine recurrence was registered in 87% and 21% of them, respectively (p = 0.001) (Table 2).

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PFO Closure Group (n = 53)</th>
<th>Control Group (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>42 ± 10</td>
<td>43 ± 11</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>5 (9%) / 48 (91%)</td>
<td>3 (10%) / 26 (90%)</td>
</tr>
<tr>
<td>&gt;1 cardiovascular risk factors</td>
<td>2 (4%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Presence of aura</td>
<td>23 (43%)</td>
<td>13 (45%)</td>
</tr>
<tr>
<td>Thrombophilia, %</td>
<td>15 (28%)</td>
<td>8 (28%)</td>
</tr>
<tr>
<td>Grading of RLS at TCCD</td>
<td>3.4 ± 0.6</td>
<td>3.3 ± 0.6</td>
</tr>
<tr>
<td>Grade 3</td>
<td>33 (62%)</td>
<td>23 (79%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>16 (30%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>4 (8%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Septal aneurysm</td>
<td>17 (32%)</td>
<td>10 (34%)</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation or n (%). Differences between the closure group and control group were not statistically significant (p > 0.05). Thrombophilia were stated if ≥1 of the subsequent thrombogenic risk factors were positive: polymorphism of factor V Leiden, polymorphism of factor II, lupuslike anticoagulant, anticardiolipin antibodies, protein C antigen, protein S, antithrombin, hyperhomocysteinemia. Grades are explained in the Methods. Septal aneurysm: diameter of the base ≥15 mm and total excursion of the septum ≥10 mm.

PFO = patent foramen ovale; RLS = right-to-left shunt; TCCD = transcranial color Doppler.

Table 2. Clinical Results According to Treatment Allocation

<table>
<thead>
<tr>
<th></th>
<th>PFO Closure Group (n = 53)</th>
<th>Control Group (n = 29)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aura</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Pre</td>
<td>23 (43%)</td>
<td>13 (45%)</td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>10 (19%)</td>
<td>9 (31%)</td>
<td></td>
</tr>
<tr>
<td>Total attacks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ (pre–post)</td>
<td>25 ± 13</td>
<td>6 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disappearance</td>
<td>18 (34%)</td>
<td>2 (7%)</td>
<td>0.007</td>
</tr>
<tr>
<td>&gt;50% reduction</td>
<td>46 (87%)</td>
<td>6 (21%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disabling attacks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ (pre–post)</td>
<td>18 ± 13</td>
<td>2 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disappearance</td>
<td>28 (53%)</td>
<td>2 (7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;50% reduction</td>
<td>47 (89%)</td>
<td>5 (17%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation or n (%). A greater reduction of total and disabling attacks was observed in the closure group compared with the control group (p < 0.001). Similarly, patients in the closure group reported a greater benefit in frequency and severity of migraine recurrence than patients in the control group.

NS = nonsignificant; pre = episodes in the 6-month evaluation period; post = episodes in the 6-month follow-up; Δ (pre–post) = difference between the number of attacks in the evaluation period and in follow-up; other abbreviation as in Table 1.

Figure 1. Frequency of Migraine Attacks at Baseline and Follow-Up

A significant reduction in frequency of total attacks was observed in the 2 groups. However, patients in the closure group exhibited a greater symptomatic improvement (patent foramen ovale closure group vs. controls: p < 0.001). Each line represents 1 patient. *6-month evaluation period versus 6-month follow-up, repeated measures statistic analysis. MT = optimized medical therapy.
attacks (from $20 \pm 12$ to $2 \pm 2$, $p < 0.001$; controls: from $15 \pm 12$ to $12 \pm 12$, $p = \text{NS}$; $p < 0.001$ between the 2 groups) (Fig. 2). Disabling attacks disappeared in 53% of PFO closure patients and 7% of controls ($p < 0.001$) (Table 2). Significant clinical improvement in severity of migraine was registered in 89% and 17% of them, respectively ($p < 0.001$) (Table 2). No significant differences in aura reduction were observed between the 2 groups (Table 2). In addition, the degree of improvement in frequency and severity of migraine recurrence after PFO closure was similar in patients with and without aura.

In the patient with residual grade 2 RLS (grade 4 before PFO closure), we observed a small ($<50\%$) decrease in total (from 28 to 19) and disabling (from 10 to 8) attacks. As regards the 2 patients with residual grade 1 RLS (grade 3 at baseline), 1 exhibited a little decrease in total attacks (from 28 to 20) and unchanged frequency of disabling attacks ($n = 15$), and the other reported a clinically significant symptomatic benefit.

After adjustment for propensity score, the significant advantage for patients in the closure group persisted in terms of migraine disappearance (odds ratio [OR]: 6.9, 95% confidence intervals [CI]: 1.5 to 32.5, $p = 0.014$), disappearance of disabling attacks (OR: 15, 95% CI: 3.2 to 70, $p < 0.001$), improvement in frequency (OR: 25.2, 95% CI: 7.6 to 83.6, $p < 0.001$), and severity of migraine attack recurrence (OR: 37.6, 95% CI: 10.4 to 135.8, $p < 0.001$).

**Discussion**

Migraine, a disorder with important socioeconomical impact, is very frequent in the Caucasian population (1). Several studies have highlighted the association between migraine and PFO. In a large study recruiting 334 migraineurs (21), prevalence of PFO has been found to be double when compared with PFO in the general population, and particularly high in the presence of aura (21). Similarly, migraine has been reported to be highly prevalent (up to 56%) in patients with PFO (22). A possible beneficial effect of PFO closure on migraine has been suggested by several both retrospective (4–10,12,13) and prospective studies (5,11). Many previous studies, however, were not controlled (4–8,12,13); moreover, migraineurs were selected from study populations with a previous cryptogenic stroke, and a possible confounding effect from antiplatelet therapy on migraine was not always considered. Finally, when retrospective, these studies were exposed to a referral bias risk.

The typical patient enrolled in most of these studies had suffered from cerebrovascular events (stroke or transient ischemic attack), presumably caused by paradoxical thromboembolism, and complained of migraine of whatsoever severity. In this setting, migraine disappeared after PFO closure in a large percentage of patients, up to 80% (7). However, a recent systematic review including 6 studies and 194 migraineurs, although confirming the improvement in migraine symptoms after PFO closure, also showed a very
low grade of evidence (2). Moreover, the recently published prospective, randomized, and sham-controlled MIST (Migraine Intervention with STARFlex Technology) trial, focused on a different clinical setting (moderate or large RLS consistent with PFO, migraine but no prior cerebrovascular events), failed to support a significant advantage of PFO closure in comparison with medical treatment (23). However, inherent methodological limitations have been outlined (24–26), as the use of contrast transthoracic echocardiography to detect PFO and quantify RLS.

The present prospective case-control study enrolled patients with an intermediate cluster of characteristics compared with previous uncontrolled studies and MIST trial. In fact, we rigorously selected patients with large RLS, moderate/severe migraine and no previous symptomatic cerebrovascular events, but with brain MRI lesions presumably due to silent ischemic episodes. Thus, our patients with high-grade RLS (associated with migraine and stroke) (22) and moderate/severe migraine had the room for significant improvement in frequency and severity of symptoms. Moreover, these patients probably constituted a group at high risk for future cerebrovascular events. In fact, multiple silent brain lesions, especially in the posterior cerebral circulation, have been detected in patients with cryptogenic stroke and a large PFO (15,16). Also, “pure” migraineurs exhibit a high frequency of unexplained brain abnormalities, and a causal link with PFO can be suggested, although an imbalance of oxygen support and consumption during migraine cannot be excluded (14). A PFO closure may then result in symptomatic relief of migraine through prevention of paradoxical microembolism or direct passage of vasoactive substances not filtered by the lungs (24).

In our study, patients treated with PFO closure significantly improved in frequency and severity of migraine recurrence. Although mild improvement was reported by some patients treated conservatively, most of them did not show a significant benefit and about one-third of them did not improve or even worsened (Fig. 3). Most importantly, only patients in the closure group reported a significant reduction of migraine severity (i.e., decrease in disabling attacks), which is crucial for quality of life. In contrast, the number of disabling attacks did not change or increased in 41% of controls (Fig. 3). Finally, in contrast to Azarbal et al. (9), we did not observe any influence of associated aura on clinical results after PFO closure.

Some methodological strengths of our study should be emphasized: PFO and RLS were carefully assessed by both TCCD and transesophageal echocardiography; a possible confounding effect of antiplatelet drugs was minimized by starting the follow-up 6 months after treatment allocation, although an effect limited to the first days after discontinuation cannot be excluded; we considered both frequency (i.e., total attacks number) and severity (i.e., disabling attacks number) of migraine recurrence, avoiding the complexities of a severity score; finally, the use of intracardiac ultrasound optimized the accuracy of well-sized devices and resulted in few residual RLS.

**Study limitations.** Some study limitations need to be recognized. Patients were not randomized but simply allocated to treatment on the basis of their consent, which may have
been influenced by personal knowledge of the link between PFO and migraine. The higher number of disabling attacks during the evaluation period in closure group than in controls may have overemphasized the clinical benefit in the first group. The medical therapy was not standardized. Our study population was relatively small, although larger than in most comparable studies. Finally, frequency and characteristics of migraine were self-reported, and different forms of headache could not have been definitively excluded.

Conclusions
A significant reduction in frequency and severity of migraine recurrence can be obtained by PFO closure in patients with large RLS and without previous symptomatic cerebrovascular events, but with silent brain lesions at MRI. However, a larger randomized trial, focused on this setting of patients with PFO, is necessary to confirm our results.

Reprint requests and correspondence: Dr. Carlo Vigna, Depart-ment of Cardiology, Casa Sollievo della Sofferenza Hospital IRCCS, Viale Cappuccini, 71013 San Giovanni Rotondo (FG), Italy. E-mail: carlovigna@libero.it.

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Key Words: patent foramen ovale closure migraine subclinical brain lesions.