Article

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Patent foramen ovale in trigeminal autonomic cephalalgias and hemicrania continua

A non-specific pathophysiological occurrence?

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ABSTRACT

Patent foramen ovale (PFO), a relatively common abnormality in adults, has been associated with migraine. Few studies also linked PFO with cluster headache (CH). To verify whether right-to-left shunt (RLS) is related to headaches other than migraine and CH, we used transcranial Doppler following microbubbles injection to detect shunts in 24 CH, 7 paroxysmal hemicrania (PH), one SUNCT, two hemicrania continua (HC) patients; and 34 matched controls. RLS was significantly more frequent in CH than in controls (54% vs. 25%, p=0.03), particularly above the age of 50. In the HC+PH+SUNCT group, RLS was found in 6 patients and in 2 controls (p=0.08). Smoking as well as the Epworth Sleepiness Scale correlated significantly with CH, smoking being more frequent in patients with RLS. PFO may be non-specifically related to trigeminal autonomic cephalalgias and HC. The headache phenotype in PFO patients probably depends on individual susceptibility to circulating trigger factors.

Key words: patent foramen ovale, right-to-left shunt, cluster headache, paroxysmal hemicrania, migraine, SUNCT, hemicrania continua.

Foramen oval patente em cefaleias trigêmino-autonômicas e hemicrania contínua: uma ocorrência fisiopatológica não específica?

RESUMO

O forame oval patente (FOP), uma anormalidade cardíaca relativamente comum em adultos, tem sido associado à enxaqueca, mas raramente às cefaléias trigêmino-autonômicas (TACs). Utilizamos o Doppler transcraniano (DTC) para detecção de shunt direito-esquerdo (SDE) em 24 pacientes com cefaléia em salvas (CS), sete com hemicrania paroxística (HP), dois com hemicrania continua (HC) e um com SUNCT; alem de 34 controles. O SDE foi mais frequente nos pacientes com CS do que nos controles (54% vs. 25% p=0,03), particularmente acima de 50 anos. No grupo HP+HC+SUNCT, o SDE foi encontrado em seis pacientes e dois controles (p=0,08). O hábito de fumar, bem como sonolência excessiva diurna foram mais frequentes em paciente com CS. O FOP pode ter importância inespecífica na fisiopatologia das TACs e HC, na dependência da susceptibilidade individual a fatores desencadeantes.

Palavras-chave: foramen oval patente, shunt direito-esquerdo, cefaléia em salvas, hemicrania paroxística, enxaqueca, SUNCT, hemicrania continua.

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The patent foramen ovale (PFO), a communication between the right and left atria, is present in around 27% of the normal adult population[1]. Although the atrial left mean pressure is mostly higher than the mean pressure at the opposite side, right-to-left shunting (RLS) may occur in these patients during transient reversals of the pressure gradient, specially with Valsalva manoeuvre and diseases leading to increased pulmonary vascular resistance[2]. PFO has been involved with varying conditions such as paradoxical embolism[3] and diving decompression syndromes[4].

Migraine is one of the most frequent primary headaches. PFO has been found to be associated with migraine with aura but not migraine without aura[5], although controversy remains on the actual role of this disorder in migraine[6]. A relatively higher PFO rate was also found in cluster headache[7-10], a distinct primary head pain disorder, suggesting that RLS could facilitate headaches in a non-specific way. However, it remains unknown whether PFO is also significantly more prevalent in other primary headaches, and what the role of this abnormality in headache pathophysiology really is. To test the hypothesis that PFO prevalence may be of importance beyond the context of migraine and is not specifically related to a particular type of primary headache, we used transcranial Doppler to collect evidence of RLS in trigeminal autonomic cephalalgias (TAC's) and hemicrania continua (HC) as compared to headache-free controls.

The objective of this work was to investigate the prevalence of right-to-left shunt and characteristics of intracranial haemodynamic in cluster headache (CH), paroxysmal hemicrania (PH), short lasting, unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and hemicrania continua patients as compared to normal controls.

METHOD

This study was approved by the University Hospital Ethics Committee at UFRJ, Rio de Janeiro (protocol 108/06). Consecutive patients suffering from cluster headache (CH; n=24); paroxysmal hemicrania (PH; n=7); short-lasting, unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT; n=1), and hemicrania continua (HC; n=2) were studied, as well as 34 controls, matched for age (±5 years) and sex. Among 41 eligible patients, 5 refused participating in the study, and two were excluded due to venous puncture difficulties. Among the initial 38 controls, two were removed because of insonation trouble and two due to age and sex incompatibility. Controls were selected among the hospital personnel provided they had no history of trigeminal autonomic cephalalgias, HC or other primary headaches. All patients and controls included assigned informed consent. TACs and HC patients were diagnosed according to the IHS 2004 criteria. They should suffer neither from co-morbid headaches nor other neurological and/or systemic diseases. None of the participants had a history of lung disease, previous thromboembolic events or other disorder potentially associated with abnormal right atrial pressure.

The Epworth sleepiness scale (ESS), an easy-to-administer questionnaire that allows objective sleepiness assessment and smoking habits were analysed and correlated with the diagnoses and the presence of PFO. EES values ≥11 are associated with sleep disturbances, including the obstructive sleep apnea syndrome[11].

Examinations were performed by 1-3 physicians, being one not blind for the diagnosis. Patient selection and diagnoses were performed by an independent neurologist. A transcranial Doppler (TCD) device (EME-Nicolet, TC-22, Bristol, Great-Britain) was used to assess the presence of RLS. The microbubbles (MB) contrast agent, prepared by alternately forcing the exchange of 9 mL isotonic saline solution and 1 mL room air between syringes through a three-way stopcock, was injected as a bolus through a 18-gauge needle inserted into the right cubital vein. Insonation of the right middle cerebral artery (MCA) was performed for MB detection in basal conditions and repeated three times, each of them following a 10 s lasting Valsalva maneuver (VM), performed 5 s after contrast injection. In order to prevent possible air embolism, VM was not performed in case of massive MB detection in the basal condition ('curtain pattern'). A four-level categorization was accepted according to MB appearance in the TCD spectrum: [a] no MB occurrence; [b] 1-20 MB; [c] >20 MB, with no curtain effect ('shower'); and [d] curtain effect, when a single MB cannot be recognized out from the background. The VM strength was controlled by the peak flow velocity of the Doppler curve. The time when the first MB appeared at the MCA level was recorded[12]. According to Jauss and Zanette, a general agreement for a cutoff interval for RLS detection does not exist. RLS was considered if at least one MB was recorded within 22 s, at either rest or following VM[12].

Data were analyzed with Epi-Info 3.5.1 for Windows. Fisher's exact, chi-square and t-tests were employed for statistical comparisons. Since differences in PFO prevalence above and below 50 years of age seemed to emerge, analyses were also performed using an arbitrary cut-off at this point. A two-sided p value of less than 0.05 was considered significant. Data are shown as mean±SD.

RESULTS

Twenty-four CH (46.8±13,7 y-o, 91.7% males. Paired controls: 46.7±14.3 y-o); 7 PH (53.2±23.5 y-o, 1 male), two HC (20 y-o, female and 35 y-o, male) and 1 SUNCT (54 y-o, male) patients have been examined. Due to the

Table. Number of cluster headache patients and controls classified in each of the four TCD recording patterns according to microbubbles detection: No Shunt: no MB occurrence; 1-20 MB; Shower: >20 MB but no curtain effect; and curtain effect. RLS were significantly more frequent in CH patients (54.2%) than in controls (25%, p=0.03).

	Cluster headache	Controls
No shunt	11	18
1-20 MB	6	0
Shower	4	6
Curtain	3	0

TCD: transcranial Doppler; MB: microbubbles; RLS: rigth-to-left shunt; CH: cluster headache.

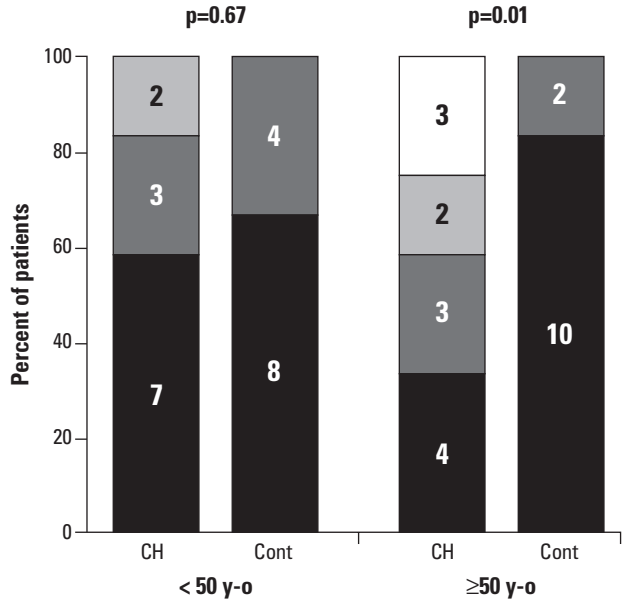

Figure. Number [y axis] of cluster headache [CH] patients and controls [CONT] classified according to four microbubbles [MB] detection patterns: No Shunt: no MB occurrence [black bars]; 1–20 MB [dark grey bars]; Shower: >20 MB but no curtain effect [light grey bars]; and curtain effect [white bars]. The first two columns show data concerning patients below 50 years of age and the last two columns represent patients above that age. p values are shown at the top for each age group comparison.

relatively small number of patients, PH+SUNCT+HC subjects were analyzed as a group (n=10, 48.1±22.6 y-o, 70% female. Paired controls: 48.6±21.7 y-o).

RLS were significantly more frequent in CH patients (54.2%) than in controls (25%, p=0.03). This difference was particularly significant above the age of 50 (CH: 66% vs controls: 16%. p=0.018). Following Valsalva maneuver, CH presented no shunt; 1-10 MB; >10 MB but no curtain; and curtain effect in respectively 45.8%, 25%, 16.7% and 12.5% of the subjects (Table). Figure depicts the subtypes of TCD recordings for the two CH age subgropus, below and after 50 years.

The frequency of RLS was also higher in the HC+PH+SUNCT group (60%) as compared to controls (20%), however, these differences were not statistically significant. Following Valsalva maneuver, HC+PH+SUNCT group no shunt; 1-10 MB; >10 MB but no curtain; and curtain effect in respectively 40%, 30%, 20% and 10% of the subjects.

We found no statistically significant differences comparing the mean flow velocity - in middle cerebral artery (MCA right and left), anterior cerebral artery (ACA right and left) - the pulsatility index (PI) and the cerebrovascular reactivity between CH patients and controls. Similar findings were observed for HC+PH+SUNCT.

Smoking was significantly more frequent in CH patients (75%) than in controls (29.2%, p=0.001). This habit did not vary according to age in this group but was more prevalent among CH patients with RLS (66.6%) than CH patients without RLS (33.4% p=0.04).

Sleepiness was more prevalent in CH (59.1%) according to the ESS than controls (20.8%, p=0.008).

DISCUSSION

We report a significantly higher prevalence of RLS in CH, especially after the age of 50. Besides, data also point to a link between RLS and other trigeminal autonomic cephalalgias - PH and SUNCT - as well as HC. These results indicate that RLS may be non-specifically linked to distinct primary headaches.

Three studies have reported on RLS in CH. Finocchi et al. used TCD to demonstrate that RLS was 2.5 times more frequent in 40 CH patients than 40 headache and cerebrovascular diseases-free controls (42.5% vs. 17.5%, p=0.029)[8]. Morelli et al. showed using TCD and transoesophageal echocardiography that RLS was significantly more frequent in CH than controls (37% vs. 18.3%, p<0.005. n=30 and 40, respectively)[9]. Dalla Volta et al. used TCD and found 14 PFO among CH patients (36.8%)[7]. These previous studies did not report on RLS prevalence differences according to age, although their overall RLS preponderances are comparable to ours and those obtained for migraine without aura. The present study is the first to address RLS in PH, SUNCT and HC. Due to the relative small number of PH, SUNCT and HC patients, a conclusive figure cannot be obtained yet for such diseases separately. However, data may indicate that PFO is also present in these other TACs.

The matter as whether PFO is implicated in the pathophysiology of primary headaches or not has become a puzzling issue. Although a positive TCD result for RLS does not necessarily indicate a PFO, this is the most probable possibility[1]. In two case control studies using TCD, PFO was initially found to be more prevalent among migraine with aura, but not migraine without aura[13,14]. Following initial reports, another study confirmed the ten-

dency of RLS / PFO to be more frequent in migraineurs[15]. In patients who suffered cryptogenic ischemic strokes, migraine was significantly more frequent among those with PFO[16]. PFO closure, however, does not necessarily stop migraine attacks[17]. According to the results of the MIST (Migraine Intervention with STARFLEX technology) trial, PFO closure in migraineurs did not reach statistical significance for both the primary (complete cessation of migraines) and secondary (a 50% reduction in migraine days) end-points[18]. The study is likely to influence the design of current trials of PFO closure and migraine, leading to longer follow-up periods and more realistic endpoints. Some individuals may even start their migraine episodes after a PFO closure[19]. It also remains to be explained why migraine with aura and migraine without aura differ in this context.

Existing evidence strongly indicates that spreading depression (SD), a neurophysiological phenomenon firstly described by Leão, may also occur in migraine without aura[20]. Various recordings obtained with different techniques reinforce the role of SD in migraine[21]. Besides, distinct migraine preventive medications share the SD-inhibiting capability[22]. It is possible that right circulation originated eliciting elements induce SD waves ultimately leading to migraine attacks after reaching a susceptible brain.

Trigeminal autonomic cephalalgias constitute a separate primary headache disorders group. TACs characteristically result in unilateral, mostly intense headache accompanied by ipsilateral autonomic phenomena such as conjunctival injection, myosis and/or tearing. Although CH shares with migraine the response to triptans and methisergide, as well as trigeminal activation as revelled by ipsilateral calcitonin-gene related peptide (CGRP) release[23], the mechanisms behind these two entities are most probably distinct. A region at the posterior hypothalamus vicinity seems to be involved in the pathophysiology of CH[24]. The fact that stimulation of this area proved to effectively reduce CH attacks[25] speaks in favour of this role. SUNCT, a disease marked by expressive autonomic signs, has also been related to activation of a posterior hypothalamic region[26]. PH, although sharing several clinical traits with CH such as intensity, unilaterality and autonomic disturbances, does respond to indomethacin, a fundamental distinction between the two disorders. Nevertheless, this disease also seems to be linked to a deep hypothalamic area[27]. Data indicate therefore that the mechanisms behind TACs predisposition may involve deep cerebral structures, as opposed to cortical SD susceptibility in migraine. Thus, if PFO does increase the frequency of different primary headache disorders by a circulating hitherto unknown element, the conclusions may be that [a] PFO is not specific for the pathophysiology of primary headaches in general and [b] PFO-triggered headaches may depend on the individual susceptibility, possibly driven among other factors by genetic backgrounds. Thus, PFO patients with lower cortical threshold for the mechanisms involved with migraine attacks would tend develop migraine, contrary to individuals with deep brain predisposition to TACs.

HC[28] is a disorder currently not grouped together with TACs, although it shares with PH the absolute indomethacin effect, suggesting at least a partially common underlying mechanism. Although few patients have been tested so far, results indicate that this condition may also be related to RLS.

Age seems to be important issues as far as PFO and headache susceptibility are concerned. An autopsy study found PFO in 27.3% of 965 hearts, with a progressive decline from 34.3% in the first three decades to 20.2% in the ninth and tenth decades of life[1]. It is possible that the stiffening of the septum primum that normally covers the PFO and the increase in left atrial pressure that occurs with age both tend to reduce the degree of RLS, which could explain the relatively reduced prevalence of PFO in older migraine patients[15]. The present study, however, found that RLS becomes even more relevant in CH after the age of 50, contrary to what has been described for migraine with aura. The reasons for such discrepancy are not understood and do not fit with the age related septum primum stiffening / left atrial pressure hypothesis. Speculatively, the age-related PFO frequency increase in cluster headache could be related to a relatively higher right atrium pressure secondary to tabagism and/or sleep apnoea, both frequent in CH, leading to a delay in PFO closure. Epidemiological data indicate that migraine starts at a much earlier age as compared to CH[29], which could influence these figures too. On the other hand, the role of PFO in determining circulatory consequences should be expected to decrease with age[15].

The reasons why primary headaches could possibly be related to PFO remain a matter of speculation. Triggering substances putatively reaching the brain after getting into the left circulation from the pulmonary bed are attractive as a pathophysiological hypothesis[15]. There are different candidates as trigger factors in this context. Emboli are naturally a possibillity. Interestingly enough, not only migraine[30], but also CH[31], have been reported to improve following oral anticoagulant treatment. On the other hand, hypoxia may be linked somehow to migraine[32] as well as CH[33], a disorder that may be treated by oxygen inhalation. Since blood bypassing the lungs may have a lower oxygen content, cluster attacks could be triggered more easily in PFO patients[10].

The association between CH and sleep has long been recognized because of the attack predilection for noctur-

nal sleep periods. A PFO implies the likelihood of microembolic passage also during nocturnal sleep in the case of obstructive apneas or other conditions mimicking the Valsalva maneuver[34].

The higher degree of sleepiness in CH subjects, an essential issue for obstructive sleep apnea syndrome diagnosis, indicate that low O_2 saturation may be of importance in this disease.

Smoking has been correlated with CH for a long time[35]. The present study confirms this association.

The smoking habit was relatively more prevalent in CH patients with RLS as compared to patients without RLS. Since CH may be triggered by low O_2 saturation[33], the higher prevalence of smoking in RLS positive CH patients, suggests that a PFO would facilitate the induction of attacks by enabling the right-to-left passage of triggering gases that would reach the predisposed brain at higher rates.

In conclusion, based on the present findings, RLS may be of importance for headache pathophysiology in a non-specific way, perhaps depending on the type of individual susceptibility to headache. The circulating trigger factor(s) cannot be identified from the available data. Further studies involving a larger number of patients are necessary to address the issue of RLS in HC, SUNCT and PH, and better establish the actual role of PFO in different primary headaches.

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