Biomedical Research 2017; 28 (20): 8608-8612 *ISSN 0970-938X*
www.biomedres.info

Role of atrial septal pouch (ASP) in migraine etiology.

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Abstract

Atrial septal pouch (ASP) is a newly defined anomaly that results in interatrial septum fusion. The aim of the present study was to compare the incidence of ASP between patients with migraine and healthy volunteers. In addition, clinical characteristics of patients with migraine with aura were reviewed in order to reveal any correlation with cardiac imaging results. This study enrolled 26 patients suffering migraine with aura and 40 healthy volunteers. Age, sex, duration of headache, frequency and duration of attack, types of aura and pain, accompanying symptoms (such as nausea, vomiting, photophobia, and phonophobia), presence of dizziness, visual analog scale score, family history of migraine, history of risk factors for atherosclerosis, availability of drugs, neurological examination findings and cardiac imaging results were recorded. The odds ratio of having ASP in the presence of migraine with aura was 38.5% which is 30% in the healthy volunteers group ($p<0.05$). Compared with the group without atherosclerotic risk, the group with the risk demonstrated higher rates of ASP. Other clinical features demonstrated no significant differences ($p>0.05$). The results of the present study suggest that ASP is a prominent risk factor for distal embolization when observed in patients with migraine with aura. Cortical spreading depression is theorized to be related with microembolisms which originated from heart.

Keywords: Aura, Migraine, Cardiac CT, ASP.

Accepted on June 20, 2016

Introduction

Migraine is a common headache syndrome that severely reduces the quality of life. Migraine without aura is the most common type of all, whereas migraine with aura affects 30% of patients [1]. The frequency of migraine is 6% for men and 15% for women [2]. Patent foramen ovale (PFO) is reportedly two times more common in individuals suffering from migraine, as established by numerous clinical studies [3-6]. Patients may experience a marked reduction in the severity of migraine, and some patients are even completely cured following the closure of PFO [7]. Atrial septal pouch (ASP) is an anatomical variation of the interatrial septum that is created by an incomplete fusion of the primum and secundum interatrial septas; it appears as a dead-end pouch on transesophageal echocardiography. Krishnan et al. [8] find that, ASP was diagnosed in 37 of 94 patients (39.3%) in an autopsy series. Patients with left atrial pouch have been reported to suffer from cryptogenic stroke [9,10]. Our literature review revealed no study that explores the incidence of left septal pouch in patients with migraine. In Our study we aimed to determine the rate and possible anatomical and functional properties of ASP in patients with migraine with aura. Cardiac imaging methods were used to determine the rate, clinical significance, and anatomical and pathophysiological properties of newly defined ASP.

Materials and Method

Study design

This study was conducted at Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital's Neurology clinic. Dışkapı Yıldırım Beyazıt Training and Research Hospital is a level 3 hospital in Capital city of Turkey. This study was a prospective case-control study. It was approved by the local ethics committee, and all patients and volunteers signed an informed consent form.

Study setting and patient population

The study enrolled 30 patients diagnosed with migraine according to the International Headache Classification 2004 criteria [11] and 44 healthy volunteers [who were scheduled to undergo coronary computed tomography (CT) angiography for chest pain]. Age, sex, duration of headache, frequency and duration of attack, type of aura, headache character (throbbing vs. squeezing/unilateral vs. bilateral), accompanying symptoms (nausea, vomiting, photophobia, and phonophobia), presence of dizziness, visual analog scale (VAS) score, family history of migraine, history of risk factors for atherosclerosis, medications, and findings of neurological examination were recorded.

Study protocol

All individuals underwent transthoracic echocardiography; some patients were also evaluated with transesophageal echocardiography, if required. Four patients from the migraine with aura group and four from the control group who were diagnosed with an interatrial septal defect were excluded. The remaining 26 patients with migraine with aura and 40 control individuals underwent cardiac CT scan using a coronary angiography protocol of a 128-section multidetector CT scanner. The individuals were administered a contrast agent (Levovist®) during scanning. The images were then examined by an expert radiologist with 5 years of experience in cardiac imaging. Contrast leakage into interatrial septum from the left side was considered diagnostic for left ASP

Statistical analysis

Study data were analyzed with SPSS for Windows 17.00 software package. Descriptive statistics were expressed as number (n), percentage (%), median, and mean ± standard deviation. The distribution of the continuous data was analyzed with Kolmogorov-Smirnov test. Pearson's Chi-square or Fisher's exact Chi-square tests were used to compare the categorical variables. The group's means for continuous data were compared using Student's t-test or Mann-Whitney-U test. $p<0.05$ was considered statistically significant.

Results

This study enrolled 26 patients with migraine with aura (24 women, 2 men) and 40 healthy volunteers (20 women, 20 men). Comparing to the control group, patient group had a significantly lower mean age ($p=0.005$). Furthermore, the patient group had a significantly lower proportion of men and higher proportion of women ($p<0.001$). Table 1 presents the demographic characteristics of the individuals in both groups.

Table 1. *Demographic properties of the patient and control groups.*

Variables	Control (n=40)	Group Patient (n=26)	Group P value
Age (years)	41.9 ± 6.8	36.8 ± 7.5	0.005
Sex			
Female	20 (50.0%)	24 (92.3%)	<0.001
Male	20 (50.0%)	2 (7.7%)	

Both patient and control groups had different age and sex distributions. Thus, corrections by age and sex were performed, and the incidence of ASP was then compared between two groups (Table 2).

Table 2. *Cardiac CT of the patient and control groups.*

	Patient (n=26)	Group Control (n=40)	Group P value
Cardiac CT			
ASP (+)	10 (38.5%)	12 (30.0%)	0.023
Normal	16 (61.5%)	28 (70.0%)	

Our patients had a mean headache duration of 6.5 years, attack frequency of four per month, and attack duration of 24 h. Twenty-four (92.3%) patients had visual aura and two (7.7%) had olfactory aura. Clinical properties of the patients are shown in Table 3.

Table 3. *Clinical characteristics of the patient group.*

Variables	Number (Total n=26)
Length of headache history (years)	6.5 (1-15)
Attack frequency per month	4 (0.08-10)
Attack duration (hours)	24 (1-160)
Pain character	
Throbbing	14 (53.8%)
Squeezing	9 (34.6%)
Both	3 (11.5%)
Localization	
Bilateral	8 (30.8%)
Unilateral	17 (65.4%)
Bilateral+unilateral	1 (3.8%)
Nausea-vomiting	
None	2 (7.7%)
Nausea only	11 (42.3%)

Both	13 (50.0%)
Dizziness	15 (57.7%)
Pain Score (VAS)	9.5 (6-10)
Photophobia-phonophobia	
No	3 (11.5%)
Photophobia only	2 (7.7%)
Both of them	21 (80.8%)
Aura type	
Visual	24 (92.3%)
Olfactory	2 (7.7%)
Family history for migraine	12 (46.2%)
Atherosclerotic risk factors	12 (46.2%)

No significant difference was observed between the subgroups with throbbing vs. squeezing headache regarding the rate of ASP on cardiac CT (p=1.000). Furthermore, the subgroups with unilateral vs. bilateral headache (p=0.182) and the subgroups with only nausea vs. both nausea and vomiting (p=0.423) exhibited no significant differences regarding the rate of ASP on cardiac CT. The subgroups with dizziness vs. no dizziness also showed no significant differences regarding the rate of ASP on cardiac CT (p=1.000). The subgroups with photophobia only vs. both photophobia and phonophobia did not significantly differ with respect to the same aspect either (p=1.000). Finally, no significant difference was detected in the rate of ASP between the subgroups with vs. without a family history of migraine (p=0.105). As the number of patients with aura was remarkably low, no analysis could be performed to determine the effect of the type of aura on the incidence of ASP.

Compared with the group without atherosclerotic risk factors, the group with risk factors had 4.667 (95% confidence interval, 1.217–17.894) times higher incidence of ASP on cardiac CT (p=0.014). Table 4 shows the incidence of ASP in the context of clinical properties in the patient group.

Table 4. *The incidence of ASP by clinical properties in the patient group.*

Variables	Cardiac CT Normal	Cardiac CT ASP (+)	P value
Pain Character			
Throbbing	9 (64.3%)	5 (35.7%)	1
Squeezing	5 (55.6%)	4 (44.4%)	
Pain localization			
Bilateral	7 (87.5%)	1 (12.5%)	0.182
Unilateral	9 (52.9%)	8 (47.1%)	
Nausea-vomiting			
Nausea only	8 (72.7%)	3 (27.3%)	0.423
Both of them	7 (53.8%)	6 (46.2%)	
Dizziness			
No	7 (63.6%)	4 (36.4%)	1
Yes	9 (60.0%)	6 (40.0%)	
Photophobia-phonophobia			
Photophobia only	1 (50.0%)	1 (50.0%)	1
Both of them	13 (61.9%)	8 (38.1%)	
Family history for migraine			
No	11 (78.6%)	3 (21.4%)	0.105
Yes	5 (41.7%)	7 (58.3%)	
Atherosclerotic risk factors			
No	12 (85.7%)	2 (14.3%)	0.014
Yes	4 (33.3%)	8 (66.7%)	

No significant differences were observed between the groups respect to the length of headache history, headache frequency per month, attack duration, and pain score (p>0.05) (Table 5).

Table 5. *Other clinical properties of the subgroups with and without ASP among the patient group.*

Variables	Cardiac CT Normal	Cardiac CT ASP (+)	P value
Length of headache history (years)	6.5 (1-15)	7 (1-15)	0.776
Attack frequency per month	3.5 (0.08-8)	3 (1-10)	0.737
Attack duration (hours)	24 (2-160)	24 (1-72)	1
Pain score	8.5 (6-10)	10 (6-10)	0.286

Discussion

The present study revealed that the incidence of ASP was significantly higher in the patient group compared with that in the control group (p=0.023). Anzola et al. [12] and Del Sette et al. [13] suggested that patients with migraine had a significantly higher incidence of PFO, which reportedly affects 20% of the general population. Cardiac and pulmonary arterial defects leading to right-to-left shunt were associated with an increased incidence of migraine [13,14].

We weren't able to find any study questioning the incidence of ASP in patients with migraine through the literature review. However, PFO reportedly increases the risk of migraine with or without aura [15]. Our study also indicates that ASP is 5.3 times more prevalent in patients with migraine comparing to the healthy population. Because of the potential release risk into the systemic circulation may become probable through a pouch opening into the left atrium, the risk of thrombus formation and embolization inside a pouch is increased in the low-flow state. In addition to providing a gateway/passage for thromboembolism, PFO is considered to cause thrombus

formation due to the blood stagnation within [16]. Given the available data, thrombus formation may not occur inside a PFO, but inside an ASP. A previous study demonstrated that thrombus formation inside a pouch opening into the left side of the heart is associated with incomplete interatrial septum fusion. Hara et al reported that thrombus formation in the left atrial pouch attached to the interatrial septum, thereby indicating potential thrombus attachment to a pouch opening into the left atrium [17]. Thrombus is formed within the left atrial process in 50% of patients with rheumatoid heart disease [18]. A pouch opening into the left atrium might become an important ground for thrombus formation in the patient group of our present study. Similarly to the previous literature reports, our study has also detected a thrombus inside the ASP in a patient.

Migraine attack with aura can complicate acute dissection of significant arteries, such as the vertebral or carotid artery [19]. Similarly, a carotid artery puncture might also trigger embolism and a migraine attack with aura [20], an event that was observed in the brains of mice during experimental studies [21]. The present study demonstrated that the incidence of ASP was significantly higher in patients with migraine with aura comparing to the control group (p=0.014). We believe that an increased incidence of ASP in patients with migraine with aura, as has been previously observed in patients with PFO, may be explained by a possible distal embolism that causes cortical spreading depression (CSD) [22]. Existing MRI studies have provided some clarity on the occurrence of CSD during migraine aura. However, MR perfusion studies need to be performed to clearly demonstrate ischemia during aura [23].

In the patient group, our study demonstrated that individuals with atherosclerotic risk factors had a significantly higher ASP rate comparing to those without such risk factors (p=0.014). In patients with migraine, the risk of microemboli and ischemic stroke is much more increased with the contribution of an already existing coagulation disorder. Local inflammation, coagulation, and thrombocyte aggregation occur in body regions affected by microemboli, thereby producing vasoactive substances. Patients with migraine have an increased risk of stroke compared with the general population, particularly at a younger age [19,24-26]. Some meta-analyses have demonstrated that patients with migraine suffer from stroke at rates in the range of 40%–60% [27-29]. The lack of any studies that particularly examine the cardiovascular disease rate in patients with migraine limits our ability to reach solid conclusions on this matter. The issue of whether ASP development is facilitated by a possible prothrombotic process caused by atherosclerotic risk factors that prevent PFO closure or, although less likely, whether it develops in the background of an atherosclerotic structure is an intriguing topic of research for future studies.

Conclusions

The results of our study support the widely accepted theory for the pathogenesis of migraine aura that suggests CSD may be caused by microemboli of cardiac origin. Increased incidence of ASP in patients suffering migraine with aura is similar to the observation for PFO in the same population may corroborate the notion that both pathologies may collaboratively increase the risk of distal embolism. Despite the presence of local alterations in the brain, the current inability to demonstrate focal ischemia during aura, might be overcome by focal perfusion studies during migraine aura. This study might uncover a novel perspective to this recently defined clinical entity and provide an inspiration for future large-scale studies that would explore the etiology of cryptogenic stroke.

References

1. William YB, Silberstein SD. Migraine and Other Headaches. St. Paul, Minn: AAN Press; 2004.
2. Rasmussen BK, Jensen R, Schroll M, Olesen J. Epidemiology of headache in a general population-A prevalence study. J Clin Epidemiol 1991; 44: 1147-1157.
3. Onarto E, Melzi G, Casilli F, Pedon L, Rigatelli G, Carrozza A, Maiolino P, Zanchetta M, Morandi E, Angeli S, Anzola GP. J Patent foramen ovale with paradoxical embolism: midterm results of transcatheter closure in 256 patients. Interv Cardiol 2003; 16: 43-50.
4. Wilmshurst PT, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. Clin Sci 2001; 100: 215-220.
5. Schwerzmann M, Nedeltchev K, Lagger F, Mattle H, Windecker S, Meier B, Seiler C. Patent foramen ovale and migraine with aura. J Am Coll Cardiol 2003; 41: 464.
6. Rigatelli G. Migraine and patent foramen ovale: connecting flight or one-way ticket? Expert Rev Neurother 2008; 8: 1331-1337.
7. Giardini A, Donti A, Formigari R, Salomone L, Palareti G, Guidetti D, Picchio FM. Long-term efficacy of transcatheter patent foramen ovale closure on migraine headache with aura and recurrent stroke. Catheter Cardiovasc Interv 2006; 67: 625-29.
8. Krishnan SC, Salazar M. Septal pouch in the left atrium: a new anatomical entity with potential for embolic complications. JACC Cardiovasc Interv 2010; 3: 98-104.
9. Wong JM, Fisher M. The potential role of the left atrial septal pouch in cryptogenic stroke. Expert Rev Cardiovasc Ther 2016; 14: 1-3.
10. Yilmaz M, Vural MG, Karcaaltınbaba M, Yoldas TK, Yilmaz MS, Kavalci C. Left-sided atrial septal pouch and risk of cryptogenic stroke. Acta Medica Mediterranea 2016; 32: 463-467.
11. Wong JM, Lombardo D, Handwerker J, Fisher M. Cryptogenic stroke and the left atrial septal pouch: a case report. J Stroke Cerebrovasc Dis 2014; 23: 564-565.
12. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders. 2nd edition. Cephalalgia 2004; 24: 159-160.
13. Anzola GP, Magoni M, Guindani M, Rozzini L, Dalla Volta G. Potential source of cerebral embolism in migraine with

aura: A transcranial Doppler study. Neurology 1999; 52: 1622-1625.

14. Del Sette M, Angeli S, Leandri M, Ferriero G, Bruzzone GL, Finocchi C, Gandolfo C. Migraine with aura and rightto-left shunt on transcranial doppler: a case-control study. Cerebrovasc Dis 1998; 8: 327-330.
15. Tobis MJ, Azarbal B. Does patent foramen ovale promote cryptogenic stroke and migraine headache? Tex Heart Inst J 2005; 32: 362-365.
16. Takagi H, Umemoto T; ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. A meta-analysis of case-control studies of the association of migraine and patent foramen ovale. J Cardiol 2015.
17. Hara H, Virmani R, Ladich E, Mackey-Bojack S, Titus J, Reisman M, Gray W, Nakamura M, Mooney M, Poulose A, Schwartz RS. Patent foramen ovale: current pathology, pathophysiology, and clinical status. J Am Coll Cardiol 2005; 46: 1768-1776.
18. Hameed A, Akhter MW, Bitar F, Sarma R, Goodwin TM, Elkayam U. Left atrial thrombosis in pregnant women with mitral stenosis and sinus rhythm. Am J Obstet Gynecol 2005; 193: 501-504.
19. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996; 61: 755-759.
20. Tzourio C, Benslamia L, Guillon B, Aidi S, Bertrand M, Berthet K, Bousser MG. Migraine and the risk of cervical artery dissection: a case-control study. Neurology 2002; 59: 435-437.
21. Lauritzen M, Skyhoj Olsen T, Lassen NA, Paulson OB. Changes in regional cerebral blood fl ow during the course of classic migraine attacks. Ann Neurol 1983; 13: 633-641.
22. Nozari A, Dilekoz E, Sukhotinsky I, Stein T, Eikermann-Haerter K, Liu C, Wang Y, Frosch MP, Waeber C, Ayata C, Moskowitz MA. Microemboli may link spreading depression, migraine aura and patent foramen ovale. Ann Neurol 2010; 67: 221-229.
23. Dalkara T, Nozari A, Moskowitz MA. Migraine aura pathophysiology: the role of blood vessels and microembolisation. Lancet Neurol 2010; 9: 309-317.
24. Sevgi EB, Erdener SE, Demirci M, Topcuoglu MA, Dalkara TA study on the effect of air micro embolism on cerebral bioelectrical activity with spectral EEG in migraine patients with aura and patent foramen ovale. J An Heart Asoc 2012; 1: e001735.
25. Onarto E, Melzi G, Casilli F, Pedon L, Rigatelli G, Carrozza A, Maiolino P, Zanchetta M, Morandi E, Angeli S, Anzola GP. Patent foramen ovale with paradoxical embolism: Mid-term results of transcatheter closure in 256 patients. J Interv Cardiol 2003; 16: 43-50.
26. Wilmshurst PT, Byrne JC, Webb-Peploe MM. Relation between interatrial shunts and decompression sickness in divers. Lancet 1989; 2: 1302-1306.
27. Windecker S, Meier B. Patent foramen ovale and atrial septal aneurysm: When and how should they be treated. ACC Curr J Rev 2002; 11: 97-101.
28. Carod-Artal FJ, Riberio L da S, Braga H, Kummer W, Mesquita HM, Vargas AP. Prevalance of patent foramen ovale in migraine patients with and without aura compared with stroke patients. A transcranial doppler study. Cephalalgia 2006; 26: 934-939.
29. Homma S, Sacco RL. Patent foramen ovale and stroke. Circulation 2005; 112: 1063-1072.

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