Original Article

Prevalence of right to Left Shunts in Japanese Patients with Migraine: A Single-center Study

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Abstract

Background: Several studies have shown an increased prevalence of right-to-left shunt (RLs) in migraine patients, particularly those with aura. However, the prevalence of RLs and its relation to Japanese patients with migraine are unknown. We investigated the prevalence of RLs in Japanese patients with migraine.

Methods: In total, 112 consecutive patients with migraine were recruited from our headache outpatient clinic. Migraine with aura (MA) and migraine without aura (MWOA) were diagnosed according to the International Classification of Headache Disorders, 3rd edition (beta-version). Contrast transcranial Doppler ultrasound was used to detect RLs, including patent foramen ovale (PFO). Then, the associations between RLs and patients' backgrounds and presence of aura were assessed.

Results: The overall prevalence of RLs and PFO in migraine patients was 54.5% and 43.8%, respectively. The prevalence of RLs and PFO in the MA group were significantly higher than in the MWOA group (RLS, 62.9% vs. 44.0%, p=0.046; PFO, 54.8% vs. 30.0%, p=0.008). There were no marked differences in the prevalence of large, middle and small shunts between MA and MWOA patients. Compared with the MWOA patients, **the** MA patients were younger (p=0.013) and had early onset age (p=0.013) and increased prevalence of photophobia (p=0.008).

Conclusion: RLs were found in over half of the Japanese patients with migraine. Our study suggests a possible link between RLs and MA.

Key words: migraine, right-to-left shunt, patent foramen ovale, transcranial ultrasonography, migraine with aura, pulmonary arteriovenous malformation

Introduction

Patent foramen ovale (PFO) is a condition in which the foramen ovale, which normally closes at birth due to the elevation in the left atrial pressure during the transition to pulmonary circulation, is left unclosed (1). It has been reported that 15%-35% of healthy people have PFO (2, 3). PFO causes the formation of right-to-left shunts (RLs) during the Valsalva maneuver or at rest. Although several diseases, such as arteriovenous malformation (AVM) or atrial septum deficits, can cause RLs, PFO is the most common underlying factor for RLs (4).

A relationship between PFO and migraine has been reported. One hypothesis is that the passage of metabolic substances or subclinical emboli through a PFO stimulates the trigeminal nerve and cerebrovascular system, evoking migraine-like headaches (5). Although several studies reported no relationship between migraine and PFO (5), 40%-70% of patients with migraine with aura (MA) have been reported to have PFO (6). Additionally, an increased prevalence of PFO has been described in patients with chronic migraine compared to the general population and other headache groups (7). An increased prevalence of RLs has been found in patients with migraine, especially those with MA, in several cross-sectional studies; however, this relationship has not been replicated in population-based studies (8, 9) and the association between migraine and RLs has not been well studied in Asian populations.

We conducted a single-center, cross-sectional study consisting of consecutive migraine patients from a headache outpatient clinic to explore the prevalence of RLs and its associated features in Japanese patients with migraine and to test our hypothesis that patients with migraine with aura are associated with the presence of RLs.

Objective and Methods

Between April 2014 and May 2016, 119 consecutive migraine patients (mean age 39.8±13.0 years, 7 men and 112 women) were recruited from our headache outpatient clinic at the

Department of Neurology of Dokkyo Medical University Hospital. Seven patients were excluded from the study: six because of a loss in permeability during transcranial Doppler (TCD) evaluation of temporal bones and one due to insufficient information about migraine. Ultimately, 112 patients (mean age 38.6±12.2 years, 6 men and 106 women) were included in our study. MA and migraine without aura (MWOA) were diagnosed by headache specialists (RT, SS and KH) in accordance with the International Classification of Headache Disorders 3rd edition (beta-version) (10). Clinical information, including smoking status and onset age of migraine; family history of migraine; sensitivity to light, sound or smell; and comorbid diseases such as hypertension, dyslipidemia and diabetes mellitus, was obtained by questioning the patients. The clinical characteristics and prevalences of RLs were compared between the MA and MWOA groups. The institutional review board of Dokkyo Medical University Hospital approved the study (IRB approved number: 25028). All of the patients provided their written informed consent to participate.

Diagnosis of right-to-left shunts

RLs was assessed in all the patients by transcranial Doppler ultrasound (TCD; Pioneer TC8080 System; Nicolet Vascular, Tokyo, Japan) with intravenous injection of agitated saline with microbubbles by trained neurologists (AI, HT and AS). The M1 portion of the right middle cerebral artery (MCA) was depicted using a 2-MHz probe securely fixed by a headband through a gap in the temporal bone window. High-intensity transient signals (HITSs) were defined as strong transient signals (within 100 msec duration) that appeared in the same direction as the blood flow, with the intensity being at least 3-dB higher than the background reflecting the blood stream, in accordance with the criteria proposed by national consensus (11, 12). The sampling volume was set to within 8 to 10 mm, and the depth was set to between 50 and 55 mm.

96 At first, prior to the intravenous injection of contrast agent, simple observation was
97 performed for 20 minutes. The HITS detection threshold volume was set to >6 dB. Then,
98 10 ml of contrast agent (a mixture of 9 ml saline and 1 ml air) was injected intravenously
99 during the Valsalva maneuver. If HITSs were detected within 10 seconds after Valsalva load
100 release, PFO was diagnosed. Next, careful observation was made to detect HITS for 3
101 minutes after Valsalva load release. If HITSs were detected within 3 minutes, additional
102 observation was made for 3 minutes. Contrast agent was then injected intravenously without
103 the Valsalva maneuver, and we continued observation for another 3 minutes. If HITSs were
104 detected without Valsalva load, PFO or pulmonary AVM (pAVM) was diagnosed (13). Large
105 shunts were defined as > 26 HITSs, and middle shunts were defined as 5-26 HITSs. The
106 same procedure was repeated 3 times for all patients (Fig. 1).
107
108 *Statistical analyses*
109 All data are described as proportions (%) and medians (range) or means (±standard deviation).
110 The patients were classified into the MA or MWOA groups based on the presence of aura.
111 Univariate analyses were conducted to compare the characteristics between the two groups.
112 The chi-square test and Mann-Whitney U test were used to compare the characteristics
113 between the MA and MWOA groups. All p-values were two-tailed, and p-values <0.05 were
114 considered significant. All statistical analyses were performed using the IBM SPSS® software
115 program for Mac, ver. 23 (Tokyo, Japan).
116

Results

Detection of RLs

A total of 112 subjects (106 women, median age, 39.0 years, range 14-74 years) underwent the TCD examination. On simple observation, prior to intravenous injection, HITSs were not detected in any patients. Next, during a 3-minute observation period after contrast agent injection with the Valsalva maneuver, HITSs were detected in 61 subjects (54.5%). With contrast agent administration at rest, HITSs were detected in 12 subjects (10.7%). Based on these results, a total of 49 subjects (43.8%) were diagnosed with PFO, and 12 subjects (10.7%) were diagnosed with PFO or pAVM (Fig. 1). The maximum numbers of HITSs per examination were as follows: 1-5 HITSs, 40 subjects; 5-26 HITSs, 7 subjects; > 26 HITSs, 14 subjects.

Comparison between MA and MWOA

Among the 112 patients with migraine, 62 had MA and 50 had MWOA. The median ages of the MA and MWOA groups were 37.5 and 40.5 years old. The MA group was significantly younger than the MWOA group (p=0.013). Similarly, the onset age was also younger in the MA patients than in the MWOA patients (p=0.013). Among the total cohort, 74 subjects (66.1%) had a family history of migraine. Photophobia (75.9%), phonophobia (74.1%), and hypersensitivity to smell (56.3%) were commonly observed. Photophobia was more frequent in the MA group than in the MWOA group (86.2% vs. 64.0%, p=0.008). However, there was no significant difference in the prevalence of phonophobia, hypersensitivity to smell, altered taste, or allodynia between the MA and MWOA groups (Table 1).

The prevalence of RLs was significantly higher in the MA group (62.9%) than in the MWOA group (44.0%) (p=0.046) (Figure 2). In addition, a higher prevalence of PFO was observed in the MA group than in the MWOA group (54.8% vs. 30.0%, p=0.008) (Table 2).

Concerning the shunt sizes, there were no differences in the prevalence of large, middle, and small shunts between MA and MWOA patients.

Discussion

In our study, we investigated the prevalence of RLs and its relationship with clinical background factors, including type of migraine. A main finding from our study is that a high prevalence of RLs (54.5%), especially in patients with aura (62.9%), was observed among Japanese patients with migraine, which is comparable to that reported in European studies (5, 6). PFO is a well-known cause of paradoxical embolism (1), and the prevalence of PFO in healthy people ranges from 15% to 35% (2, 3, 14). Patients with migraine, particularly those with MA, have been reported to have an increased prevalence of PFO compared to individuals without migraine (6, 15, 16). A recent meta-analysis showed that PFO is associated with 2.5-fold total migraine and 3.4-fold MWA prevalence, but not with MWOA prevalence (17) In our study, we confirmed increased the prevalence of PFO in the MA group compared with the MWOA group (62.9% vs. 44.0%, p=0.046), in line with the results of previous studies (15, 17).

Increased prevalence of photophobia in MA patients compared with MWOA patients was observed in our study, which is in agreement with the findings from a study of 5,758 adult residents in Japan (18) that showed a photophobia rate of 43.9% and 17.9% in Japanese patients with MA and MWOA, respectively. The prevalence of RLs and PFO was significantly increased in the MA group compared with the MWOA group. However, there was no marked difference in the shunt sizes between the groups in our study. Schwerzmann et al. (19) reported increased rates of moderate or large shunts in the migraine group compared with control groups. Contrary to our report, Yang et al. (20) showed increased rates of total and large RLs but not small RLs in patients with MA compared with MWOA. As for intrapulmonary RLs, van Gent et al. (21) reported the increased prevalence of large shunts in MA patients compared with MWOA patients. These differences might be due to discrepancies in methodologies or populations.

Regarding the mechanism underlying the potential relationship between PFO and migraine, PFO may allow vasoactive chemicals, such as serotonin and endothelin, or embolic material to bypass the pulmonary filter and reach the cerebral circulation to induce a migraine attack (15, 22). Additionally, paradoxical air microemboli through the PFO may induce cerebral electrical activity, triggering migraine attacks (23).

The effect of PFO closure on migraine has also been controversial. In several studies, PFO closure has successfully reduced the intensity and severity of migraine attacks (24), while in a double-blind randomized study that included with migraine, PFO closure failed to reduce migraine intensity and severity (9). Further discussions are needed in this point.

Several limitations associated with the present study warrant mention. First, this study used a cross-sectional design, and healthy controls were not included. According to previous studies, 15%-35% of healthy Caucasian and African-descent subjects have PFO (2, 3). To our knowledge, there has been no clinical study evaluating the PFO prevalence in healthy Japanese subjects. One autopsy study showed the PFO prevalence to be 13.6% in 109 Japanese adults (mean age 69 years) and even lower (7.0%) in those ≤ 59 years of age (25). Second, not all patients with migraine who were seen in our hospital underwent a TCD examination; therefore, selection bias might have affected the study's results. The male:female ratio is lower in our study (1:16) than in a population-based study of migraine patients in Japan (1:3.6) (26). Third, MA patients were younger and had earlier migraine onset MWOA patients. Although the prevalence of PFO decreases with age (14), given that the age gap between the MA and MWOA groups was only three years, we believe the influence of age difference had little impact on the RLs prevalence.

Conclusions

RLs were found in over half of a cohort of Japanese patients with migraine. Our study

suggests a possible link between RLs and MA in Japanese.

Abbreviations

RLs: Right to left shunts; MA: Migraine with aura; MWOA: Migraine without aura; PFO: Patent foramen ovale; pAVM: pulmonary arteriovenous malformation; TCD: transcranial Doppler; MCA: Middle cerebral artery; HITS: High-intensity transient signals; TTH: Tension type headache

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

AI contributed to the study concept and design; the diagnosis of the patients; and the acquisition, analysis, and interpretation of the data and drafted the manuscript. KS and HT contributed to the study concept and design; the diagnosis of the patients; the acquisition, analysis, and interpretation of the data; and the manuscript revision. RT, AS, and SS contributed to the study concept and design and data acquisition. KH contributed to the study concept and design and supervised the study. All authors read and approved the final manuscript.

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References

1. Windecker S, Stortecky S, Meier B. Paradoxical embolism. J Am Coll Cardiol **64**:403-415, 2014.
2. Angeli S, Del Sette M, Beelke M, Anzola GP, Zanette E. Transcranial Doppler in the diagnosis of cardiac patent foramen ovale. Neurol Sci **22**:353-356, 2001.
3. Homma S, Sacco RL. Patent foramen ovale and stroke. Circulation **112**:1063-1072, 2005.
4. Kerut EK, Norfleet WT, Plotnick GD, Giles TD. Patent foramen ovale: a review of associated conditions and the impact of physiological size. J Am Coll Cardiol **38**:613-623, 2001.
5. Sathasivam S, Sathasivam S. Patent foramen ovale and migraine: what is the relationship between the two? J Cardiol **61**:256-259, 2013.
6. 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 **52**:1622-1625, 1999.
7. Nahas SJ, Young WB, Terry R, et al. Right-to-left shunt is common in chronic migraine. Cephalalgia **30**:535-542, 2010.
8. Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. Cephalalgia **28**:531-540, 2008.
9. Tariq N, Tepper SJ, Kriegler JS. Patent Foramen Ovale and Migraine: Closing the Debate-A Review. Headache **56**:462-478, 2016.
10. Headache Classification Committee of the International Headache S. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia **33**:629-808, 2013.
11. Jauss M, Zanette E. Detection of right-to-left shunt with ultrasound contrast agent and

246 transcranial Doppler sonography. Cerebrovasc Dis **10**:490-496, 2000.
247 12. Ringelstein EB, Droste DW, Babikian VL, et al. Consensus on microembolus
248 detection by TCD. International Consensus Group on Microembolus Detection.
249 Stroke **29**:725-729, 1998.
250 13. The Joint Committee of "The Japan Academy of Neurosonology" and "The Japan
251 Society of Embolus Detection and Treatment" on Guideline for Neurosonology.
252 Exploration for embolic sources by transesophageal echo cardiography.
253 Neurosonology **19**:132-146, 2006.
254 14. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale
255 during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin
256 Proc **59**:17-20, 1984.
257 15. Dalla Volta G, Guindani M, Zavarise P, Griffini S, Pezzini A, Padovani A. Prevalence
258 of patent foramen ovale in a large series of patients with migraine with aura, migraine
259 without aura and cluster headache, and relationship with clinical phenotype. J
260 Headache Pain **6**:328-330, 2005.
261 16. Ferrarini G, Malferrari G, Zucco R, Gaddi O, Norina M, Pini LA. High prevalence of
262 patent foramen ovale in migraine with aura. J Headache Pain **6**:71-76, 2005.
263 17. Takagi H, Umemoto T, Group A. A meta-analysis of case-control studies of the
264 association of migraine and patent foramen ovale. J Cardiol **67**:493-503, 2016.
265 18. Takeshima T, Ishizaki K, Fukuhara Y, et al. Population-based door-to-door survey of
266 migraine in Japan: the Daisen study. Headache **44**:8-19, 2004.
267 19. Schwerzmann M, Nedeltchev K, Lagger F, et al. Prevalence and size of directly
268 detected patent foramen ovale in migraine with aura. Neurology **65**:1415-1418, 2005.
269 20. Yang Y, Guo ZN, Wu J, et al. Prevalence and extent of right-to-left shunt in migraine:
270 a survey of 217 Chinese patients. Eur J Neurol **19**:1367-1372, 2012.

21. van Gent MW, Mager JJ, Snijder RJ, et al. Relation between migraine and size of echocardiographic intrapulmonary right-to-left shunt. Am J Cardiol **107**:1399-1404, 2011.

22. Borgdorff P, Tangelder GJ. Migraine: possible role of shear-induced platelet aggregation with serotonin release. Headache **52**:1298-1318, 2012.

23. Sevgi EB, Erdener SE, Demirci M, Topcuoglu MA, Dalkara T. Paradoxical air microembolism induces cerebral bioelectrical abnormalities and occasionally headache in patent foramen ovale patients with migraine. J Am Heart Assoc **1**:e001735, 2012.

24. Rigatelli G, Dell'Avvocata F, Ronco F, et al. Primary transcatheter patent foramen ovale closure is effective in improving migraine in patients with high-risk anatomic and functional characteristics for paradoxical embolism. JACC Cardiovasc Interv **3**:282-287, 2010.

25. Kuramoto J, Kawamura A, Dembo T, Kimura T, Fukuda K, Okada Y. Prevalence of Patent Foramen Ovale in the Japanese Population- Autopsy Study. Circ J **79**:2038-2042, 2015.

26. Sakai F, Igarashi H. Prevalence of migraine in Japan: a nationwide survey. Cephalalgia **17**:15-22, 1997.

290 **Figure legends**

291 Figure 1: Flowchart for the diagnosis of right-to-left shunts. RLs: Right-to-left shunts; TCD:
292 transcranial Doppler; HITS: High-intensity transient signals; PFO: Patent foramen ovale.

293

294 Figure 2: Prevalence of RLs in the MWOA and MWA groups. MA: Migraine with aura;
295 MWOA: Migraine without aura; RLs: Right-to-left shunts. Chi-square test.