Prevalence and extent of right-to-left shunt in migraine: a survey of 217 Chinese patients

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Background: Recently, contrast-enhanced transcranial Doppler (cTCD) studies have shown that right-to-left shunt (RLS) may be a risk factor for migraine in Westerners; however, limited data in the literature describes the prevalence of RLS in Chinese patients with migraine.

Objective: To assess the prevalence of RLS in patients with migraine in China and to evaluate the relationship between the extent of RLS and migraine.

Methods: A total of 217 consecutive patients with a diagnosis of migraine and 100 volunteers were recruited. cTCD was used to assess the prevalence and the extent of RLS in all subjects.

Results: In the migraine group, the rate of positive RLS was 44.2% (96/217), with 23.5% (51/217) of these being large. In the healthy group, 28.0% (28/100) were positive for RLS overall, and 5.0% (5/100) were large ($P = 0.006$; $P < 0.001$). In patients having migraines with aura (MwA), 66.1% (39/59) were positive for RLS overall, and 37.3% (22/59) were large, which was significantly higher when compared with the healthy group ($P < 0.001$; $P < 0.001$); in patients having migraines without aura (MwoA), 36.1% (57/158) were positive for RLS overall, and 18.4% (29/158) were large, which was against significantly higher ($P < 0.001$; $P = 0.003$). In the MwoA group, the large RLS rate was also higher than in the healthy group ($P = 0.002$).

Conclusions: A close correlation has been documented between RLS and migraine, especially MwA, but these relationships exist only when the shunts were large.

Introduction

Migraine is a chronic neurological disorder characterized by moderate to severe headaches, and it might have one or all symptoms, including photophobia, throbbing, nausea, and vomiting. It has an estimated prevalence of 8–13% in the Western population, with more than 55 million Europeans and Americans experiencing migraine [1,2]. However, the spectrum of diseases varies in different ethnic groups, and earlier studies have observed that Chinese people have a much lower migraine prevalence (0.987–3.9%) than Westerners [3,4].

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Migraine is a common and complex brain disorder. The underlying pathogenesis is not well understood. Recently, contrast-enhanced transcranial Doppler (cTCD) studies have shown that right-to-left shunt (RLS), usually attributed to a patent foramen ovale (PFO), may be a risk factor for migraine and, in particular, migraine with aura (MwA) [5,6]. Previously published studies found that RLS is quite common in the general population in Western countries, with a prevalence of approximately 10% to 25% depending on the population studied and the methodology used for diagnosis [7].

The aim of this study was to assess the prevalence of RLS in migraine, MwA, migraine without aura (MwoA) patients, and healthy people in China to evaluate the relationship between the extent of RLS and migraine. To the best of our knowledge, this is the first report describing the prevalence of RLS in Chinese patients with migraine.

Methods

Participants

The study design was approved by the Ethics Committee of the First Norman Bethune Hospital of Jilin University. Informed consent was obtained from all subjects. From April 2010 to February 2011, two hundred and seventeen consecutive patients with a diagnosis of migraine (35.03 ± 12.73 years old, 63 males, 154 females) were recruited from the Department of Neurology at the First Norman Bethune Hospital of Jilin University. Patients with Migraine were divided into two groups: MwA (59 cases, 32.15 ± 13.26 years old, 19 males, 40 females) and MwoA (158 cases, 36.11 ± 12.40 years old, 44 males, 114 females). Each patient was diagnosed with migraines by two neurologists according to the International Headache Society Criteria [8]. One hundred healthy volunteers without migraine (medical students, nurses, and doctors in our department) were recruited as normal controls. The average age of the healthy group was slightly younger than the migraine and MwoA groups, but there were no significant differences in gender between the four groups. The average age in the various groups were all within 30–40 years old (Table 1).

Subjects with stenotic intracranial or extracranial arteries or intracranial abnormalities diagnosed with transcranial Doppler (TCD; EMS-9, Delica, China), carotid ultrasound (IU22; Phillips, Andover, MA, USA), or magnetic resonance imaging (1.5T-MRI, GE, Waukesha, WI, USA) were excluded. The clinical workup consisted of a thorough physical examination, laboratory tests including liver and kidney function tests, hematology profiles, TCD, carotid ultrasound, cTCD (MultiDop ×4; DWL, Sipplinghen, Germany), and MRI.

cTCD protocol

An 18-gauge needle was inserted into the cubital vein in the supine position. Insonation of one middle cerebral artery (MCA) using TCD was performed. Contrast agent was prepared using 9 ml isotonic saline solution, 1 ml air, and a drop of the patient's blood that was vigorously mixed between two 10-ml syringes via a 3-way stopcock [9–11]. After 30 mixing cycles, the contrast agent was injected as a rapid bolus [9]. The first injection was performed during normal respiration (rest), and the second injection was performed 5 s prior to the start of a ten-second valsalva maneuver (VM). The strength of the VM was measured by peak flow velocity along the Doppler curve. The time when the first microbubble (MB) appears at the MCA level was noted [9,10]. The maximum number of bubbles recorded from the MCA in each case either during normal breathing or after VM was taken as the estimate of the maximum degree of shunt [12].

Two ultrasound technologists and one neurologist, each blinded to the diagnosis of migraine, were designated to assess the prevalence and extent of RLS in all subjects. On the basis of the standards reported by Jauss and Serena, a four-level RLS categorization based on the MB count was applied as follows: none, 0 MBs (negative result, Fig. 1a); mild, 1–10 MBs (Fig. 1b); moderate, $10 < \text{MBs} \leq 25$ (Fig. 1c); and large, >25 MBs (Fig. 1d) [9,10]. RLS was considered latent if it occurred only after VM and permanent when it occurred also at rest. RLS was considered to be small if mild or moderate RLS was detected [9,13,14].

Statistics

The statistical program for social sciences version 12.0 (SPSS; IBM, West Grove, PA, USA) was used to analyze all the data. Differences between groups were analyzed with the *t*-test for continuous variables and the chi-squared test for nominal variables. All tests were two-tailed, and the level of significance was set at $P < 0.05$.

Results

In the migraine group, 44.2% (96 of 217) had a positive RLS result, 53 of 96 cases were permanent (55.2%) and 43 cases were latent (44.8%). In the MwA group, 66.1% (39 of 59) had a positive RLS result, 22 cases were permanent (56.4%) and 17 cases were latent (43.6%). In the MwoA group, 36.1% (57 of 158) had a positive result, 31 cases were permanent (54.4%) and 26 cases were latent (45.6%). In the healthy group, 28.0% (28 of 100) had a positive RLS result, 17 cases were permanent (60.7%) and 11 cases

Table 1 Demographic features of the study participants

	Migraine *n* = 217	MwA group *n* = 59	MwoA group *n* = 158	Healthy group *n* = 100
Age, y	35.03 ± 12.73	32.15 ± 13.26	36.11 ± 12.40	31.93 ± 10.42
Female	154 (71.0%)	40 (67.8%)	114 (72.2%)	65 (65.0%)

MwA, migraines with aura; MwoA, migraines without aura.

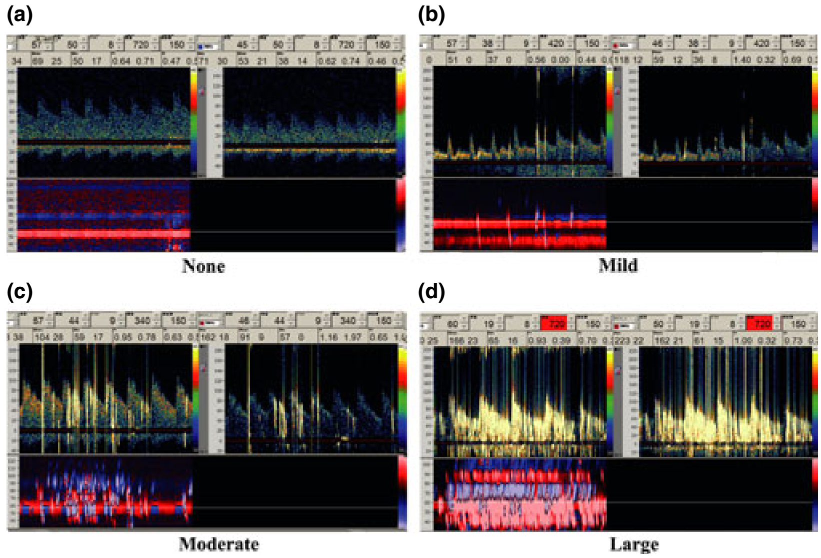

Figure 1 The four-level right-to-left shunt categorization based on the microbubble (MB) count. None: 0 MBs (negative result, a); mild: 1–10 MBs (b); moderate: 10 < MBs ≤ 25 (c), and large: >25 MBs (d).

were latent (39.3%). There were no significant differences in permanent and latent in the various groups (Table 2). In the following text, we analyzed the relationship between maximum degree of shunt and migraine (MwA and MwoA) in the various groups.

Table 2 Total positive rates, permanent, and latent right-to-left shunt (RLS) rates in the various groups

	Total positive rate (%)	Permanent RLS rate (%)	Latent RLS rate (%)
Migrainegroup	44.2 (96/217)	55.2 (53/96)	44.8 (43/96)
MwA group	66.1 (39/59)	56.4 (22/39)	43.6 (17/39)
MwoA group	36.1 (57/158)	54.4 (31/57)	45.6 (26/57)
Healthy group	28.0 (28/100)	60.7 (17/28)	39.3 (11/28)

MwA, migraines with aura; MwoA, migraines without aura.

Migraine (MwA and MwoA) and healthy groups

The patients in the migraine group were a little older than those in the healthy group ($t = 2.29$, $P = 0.02$, Table 1). There were no significant differences in gender between the two groups ($\chi^2 = 1.14$, $P = 0.29$, Table 1).

Right-to-left shunt was detected in 44.2% of the patients in the migraine group (96 of 217), 121 cases were negative (55.8%); 33 cases were mild (15.2%), 12 cases were moderate (5.5%), and 51 cases were large (23.5%) (Fig. 2a). In the healthy group, 28.0% (28 of 100) had a positive RLS result, and 72 cases were

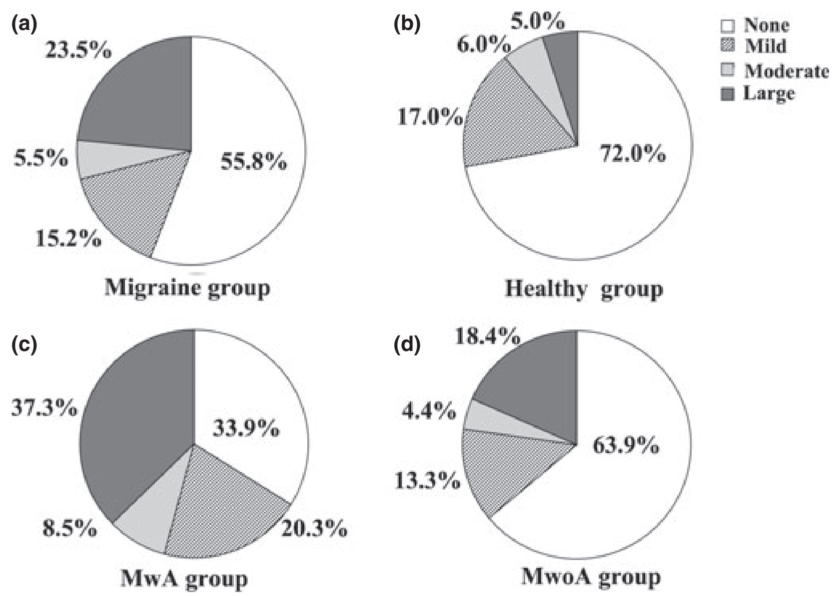

Figure 2 The percentage of migraine (a), healthy (b), MwA (c), MwoA (d) groups based on the four RLS levels. The relative total positive RLS rates (stripe, light gray and dark gray) in the groups were as follows: migraine group > healthy group; MwA group > healthy group and MwoA group; MwoA group healthy group. The relative large RLS rates (dark gray) in the groups were as follows: migraine group, MwA group, MwoA group > healthy group; MwA group > MwoA group, the small RLS rates (stripe and light gray) were similar.

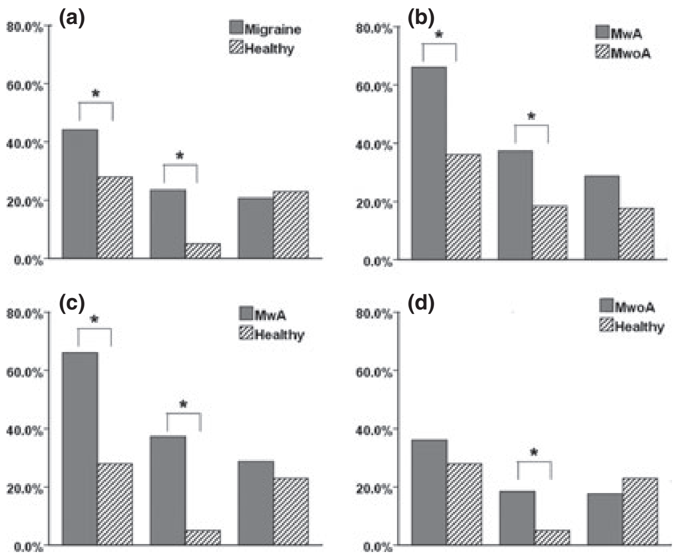

Figure 3 The positive rates, large right-to-left shunt (RLS) rates and small RLS rates in the various groups. The positive and large RLS rates in the migraine group were significantly higher than those in the healthy group (a). The positive and large RLS rates in the migraines with aura (MwA) group were significantly higher than those in the migraines without aura (MwoA) group (b) and healthy group (c). Although the positive RLS rate in the MwoA group was similar to that in the healthy group (d), the large RLS rate was also higher in the MwoA group than in the healthy group (d).

negative (72.0%); 17 were mild (17.0%), six were moderate (6.0%), and five were large (5.0%) (Fig. 2b). The total positive and large RLS rates in the migraine group were significantly higher than those in the healthy group (χ^2 = 7.58, P = 0.006; χ^2 = 16.11, P < 0.001), but the small RLS rate was similar between the two groups (χ^2 = 0.21, P = 0.65) (Fig. 3a).

MwA and MwoA group

The patients in the MwA group were younger than those in the MwoA group (t = 2.05, P = 0.04). There were no significant differences in gender between the two groups (χ^2 = 0.40, P = 0.53, Table 1).

RLS was detected in 66.1% of the patients in the MwA group (39 of 59), and 20 cases were negative (33.9%); 12 cases were mild (20.3%), five cases were moderate (8.5%), and 22 cases were large (37.3%) (Fig. 2c). In the MwoA group, 36.1% (57 of 158) had a positive result, 101 cases were negative (63.9%); 21 cases were mild (13.3%), seven cases were moderate (4.4%), and 29 cases were large (18.4%) (Fig. 2d). The total positive and large RLS rates in the MwA group were significantly higher than those in the MwoA group (χ^2 = 15.7, P < 0.001; χ^2 = 8.57, P = 0.003), but the small RLS rate was similar between the two groups (χ^2 = 3.22, P = 0.07) (Fig. 3b).

MwA and healthy groups

There were no significant differences in age (t = 0.11, P = 0.91) and gender (χ^2 = 0.13, P = 0.72) between the two groups (Table 1).

The total positive and large RLS rates in the MwA group were significantly higher than those in the healthy group (χ^2 = 22.09, P < 0.001; χ^2 = 27.44, P < 0.001), but the small RLS rate was similar between the two groups (χ^2 = 0.67, P = 0.41) (Fig. 3c).

MwoA and healthy groups

The average age of patients in the migraine group was slightly higher than the age of patients in the healthy group (t = 2.91, P = 0.04). There were no significant differences in gender between two groups (χ^2 = 1.47, P = 0.23) (Table 1).

The total positive and small RLS rates in the MwoA group were similar to those in the healthy group (χ^2 = 1.81, P = 0.18; χ^2 = 1.08, P = 0.30), but the large RLS rate in the MwoA group was significantly higher than that in the healthy group (χ^2 = 9.55, P = 0.002) (Fig. 3d).

Discussion

Migraine headache is a chronic disabling condition that affects approximately 6% of men and 15% to 18% of women [2,7,15]. Migraine is thought to be caused by both hereditary and environmental factors and is believed to have neurogenic and neurovascular origins; however, its underlying pathogenesis is not well understood [7]. Several studies have recently reported that patients with migraine have an almost twofold greater prevalence of an RLS compared with the general population [7,16,17]. However, other studies have noted that the prevalence of RLS was similar in patients with and without migraines [7,18], whereas other studies found that RLS was associated with MwA but not with MwoA [19–21]. In our research, we found there is a close correlation between RLS and migraine, especially MwA, but these relationships exist only when the shunts were large.

In 1998, Del Sette *et al*. [16] studied 44 patients with MwA and 50 controls. Eighteen of these 44 patients with migraine (41%) showed RLS compared with eight of 50 controls (16%) ($P < 0.005$), and thus, they concluded that the prevalence of RLS in MwA patients was significantly higher than in normal controls. In 1999, Anzola *et al*. [19] found that PFO was associated with MwA but not with MwoA. Later, Anzola and colleagues performed a case–control study including 113 MwA patients, 53 MwoA patients, and 25 age-matched non-migraine subjects and came to the same conclusion [20,21]. In 2005, Schwerzmann *et al*. [5] assessed the relationship between the size of RLS and MwA and found that a small shunt was equally prevalent in MwA patients [10% (95% CI 5–18%)] and controls [10% (95% CI 5–18%)], but a moderately sized or large shunt was found more often in the MwA group [38% (95% CI 28–48%) vs. 8% (95% CI 2–13%) in controls; $P < 0.001$]. Recently, Garg *et al*. found that the prevalence of PFO was similar in subjects with migraine and healthy subjects (26.4% vs. 25.7%; odds ratio, 1.04; 95% confidence interval, 0.62–1.74; $P = 0.90$). In addition, there was no difference in PFO prevalence between the MwA and MwoA groups (26.8% vs. 26.1%; odds ratio, 1.03; 95% confidence interval, 0.48–2.21; $P = 0.93$) [7].

In this research, we studied 217 migraine patients and 100 healthy Chinese people. We found that the positive rate in MwA patients was 66.1%, similar to that of Westerners (41–72%), but the large RLS rate was significantly higher than the rates reported by Schwerzmann (37.3% vs. 27%). When we analyzed the total positive rates, we found that there were significant differences between the migraine and healthy groups, the MwA and MwoA groups, and the MwA and healthy groups, but not between the MwoA group and the healthy group (44.2% vs. 28.0%, $P < 0.05$; 66.1% vs. 28.0%, $P < 0.05$; 66.1% vs. 36.1%, $P < 0.05$; 36.1% vs. 28.0%, $P > 0.05$). (Figs 2 and 3). Interestingly, in all groups, the large RLS rates (dark gray) were significantly different among the groups, but the small RLS rates (stripe and light gray) were similar (Figs 2 and 3). It is possible that large RLSs are responsible for migraine.

The mechanisms of RLS and migraine are not well understood. One theory states that subclinical emboli and metabolites from the venous system circumvent the lungs and directly enter the systemic circulation, causing irritation of the trigeminal nerve and cerebrovascular system, and thus leading to migraine [22,23]. Another possible mechanism could be transient hypoxemia caused by the PFO, causing subclinical infarcts in the brain, leading to irritation and a propensity for migraines [22,24].

Our study describes the characteristic features of RLS in migraine patients (MwA and MwoA patients) and healthy people in China and evaluates the relationship between the extent of RLS and migraine. To the best of our knowledge, this is the first report that describes the prevalence of RLS in the Chinese population, and our research expands the spectrum of RLS findings. In this research, we tried to select the hospital staff to match the migraine group with respect to age and gender, because of the students accounted for a large proportion of our volunteers; the average age of the healthy group was slightly younger than the migraine and MwoA groups, but there were no significant differences in gender between the four groups. The average age in the various groups were all within 30–40 years old, so there were no significant age-related differences in the results. Simultaneously, because transthoracic echocardiography is a half-invasive examination, many patients refused to do it. We did not have enough appropriate data to analyze this part, so the proportion of patients between PFO and pulmonary arteriovenous fistula is not possible to know, but because of the cTCD can detect the all RLS, this is also a meaningful work. Further studies are thus warranted to explore the correlation between PFO and migraine.

Conclusions

A close correlation has been documented between RLS and migraine, especially MwA, but these relationships exist only when the shunts were large.

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