



## Migraine with aura and TCD bubble-test: The significance of positive result

Migrena sa aurom i TKD *bubble* test: značaj pozitivnog rezultata

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### Abstract

**Background/Aim.** The association between the right-to left shunt (RLS) and migraine with aura (MA) has been proven so far. The aim of this study was to determine if the presence of RLS detected as a result of transcranial doppler (TCD) bubble-test, makes any difference in clinical presentation, aura and headache in patients with MA. **Methods.** A single-group descriptive study was conducted on 153 patients diagnosed with MA. TCD bubble-test was performed on 135 of them. The recorded demographic and clinical features of patients were analyzed and compared with the results of the TCD bubble test. **Results.** In the group of 135 patients, 88 (65.2%) had positive TCD bubble-test. The difference in the investigated clinical features of patients of the patients and aura between the patients with and without RLS, was not found. **Conclusion.** The results of our study confirm a high prevalence of right-to-left shunt in patients with MA, but the clinical relevance of this association was not shown.

### Key words:

migraine with aura; ultrasonography, doppler, transcranial; diagnosis.

### Apstrakt

**Uvod/Cilj.** Udruženost desno-levog šanta (*right-to-left shunt* – RLS) i migrene sa aurom (MA) je poznata. Cilj ove studije bio je da se odredi da li prisustvo RLS otkriveno transkranijalnim doplerom (*transcranial doppler* – TCD) utiče na kliničku sliku, auru i glavobolju bolesnika sa MA. **Metode.** Ova deskriptivna studija sprovedena je na grupi od 153 bolesnika sa MA. Test TCD *bubble* test urađen je kod njih 135. Demografske i kliničke karakteristike bolesnika analizirane su i upoređene sa rezultatima TCD *bubble* testa. **Rezultati.** Od 135 bolesnika, kod 88 (65,2%) TCD *bubble* test bio je pozitivan. Nije utvrđena razlika u ispitivanim kliničkim osobinama bolesnika i aure kod bolesnika sa i bez RLS. **Zaključak.** Rezultatima ove studije potvrđena je visoka prevalencija RLS kod bolesnika sa MA. Klinička značajnost ove udruženosti, međutim, nije utvrđena.

### Ključne reči:

migrena sa aurom; ultrasonografija, dopler transkranijumska; dijagnoza.

### Introduction

The association between the cardiac right-to left shunt (RLS) and migraine with aura (MA) has been widely examined<sup>1-6</sup> and shown that there is a relationship between migraine with aura and patent foramen oval (PFO). The prevalence of PFO in the MA patients is around 50% according to results of different studies, in contrast to approximately 20% in the migraine without aura patients and even less in healthy control subjects. The tendency of paradoxical emboli for the posterior circulation<sup>7,8</sup> was the basis for the hypothesis about causality of RLS and the cortical spreading depression originating in occipital cortex with subsequent, the most common,

visual aura. According to the results of some authors, patients with migraine who have RLS tend to recognize activities that can cause Valsalva's manoeuvre, increasing the extent of shunt as a trigger of their migraine attacks<sup>9</sup>. Nevertheless, a prospective, multicenter, randomized, double blind, placebo-controlled trial revealed no casual relationship between PFO closure and reduction in the number and severity of headache attacks in patients with MA<sup>10</sup>. The pulmonary RLSs, with arteriovenous malformations background, are associated with a high migraine prevalence, as well<sup>11-13</sup>.

The aim of this study was to determine if the presence of RLS detected as a result of transcranial Doppler (TCD)

bubble-test is related to demographic features of patients with MA or the clinical presentation of aura in them.

## Methods

A single-group, descriptive study was conducted over 153 patients diagnosed with MA, selected from specific outpatient visits for headaches during the period of four years, from 2008 to 2012. Written informed patient consent was obtained from all the examined subjects. Research protocol of the study was approved by the review board of the Neurology Clinic, Clinical Center of Serbia, Belgrade.

All the patients included in the study met the International Headache Society (IHS) criteria for typical aura with migraine headache (diagnostic criteria 1.2.1)<sup>14</sup>. The demographic features (age at the time of examination, age at the time of headache onset, gender) data about family history of migraine and cerebrovascular disorders were recorded together with the duration and symptoms of aura reported by the patients. According to diagnostic IHS criteria aura was diagnosed as visual or sensory, and aura with both, visual and sensory symptoms was labeled as complex aura. Other transitory cortical dysfunctions experiencing regularly during aura, meaning disturbances in color naming, object and face recognition, memory, speech, calculation, spatial orientation and praxia, were also recorded.

The RIMED Digi-Lite (RIMED, Israel), dual channel TCD system was used in the present study. The insonation was performed through the pre-auricular acoustic bone windows according to a standard approach using 2 MHz transducers to visualize the middle cerebral artery (MCA). Bilateral monitoring was performed with each probe held in place over a temporal bone by the head frame. The MCA gate was selected for each spectrogram and the continuous recording and counting of bubble embolic signals was provided by a computer hard disk. All embolic tracks were counted in the bilaterally insonated MCA from a depth of 40 mm to 75 mm. In all the patients, the TCD bubble-test was performed in the supine position with the head inclined forward for the 30 degrees. At least 2 contrast bolus injections with 9 mL of saline, 1 mL of air were agitated and mixed with the small amount of the patient's blood, administered into an antecubital vein. The first injection was performed during normal respiration, the second injection was performed immediately

prior to non-calibrated Valsalva and if no embolic tracks were detected, additional injections were made while the patient performed the second non-calibrated Valsalva. TCD bubble-test was considered to be positive if at least 1 microbubble was detected during the first 12 seconds after injection<sup>15</sup>. To grade RLS, a 6-level logarithmic scale was used for both resting and Valsalva injections<sup>16</sup>.

The recorded demographic and clinical features were analyzed and compared with results of TCD bubble-test.

The data are presented as arithmetic mean or as percentages. The Kolmogorov–Smirnov test was applied to assess the normality of the studied continuous data. Independent-samples *t*-test and  $\chi^2$ -test were used to compare data between the two groups. The significance level for the analysis was set at 5% ( $p < 0.05$ ).

## Results

TCD bubble-test was performed in the 135 of 153 studied patients diagnosed with MA. The group of 18 patients did not undergo this test due to inadequacy of the bone windows. Positive TCD bubble-test was recorded in 88 (65.2%) of the patients. On a 6-level logarithmic scale that was used to grade RLS, 34 (25.2%) of the patients had RLS grade I, 17 (12.6%) grade II, 27 (20.0%) grade III, 9 (6.7%) grade IV and only 1 (0.7%) patient grade V.

The patients with positive TCD bubble-test, comparing to those with a negative test result, did not show any difference in gender, age at the time of examination and in age at the time of migraine onset (Table 1). Migraine without aura was present in approximately one quarter of the patients and family history of migraine in half of them in both groups (Table 1).

There were no differences between the two groups of the patients in regard to duration of aura, as well as aura symptoms (Table 2). In both groups, the most common type of aura was visual reported by more than 90% of patients, followed by sensory symptoms. More than half of the patients in both groups had complex aura, and the other cortical dysfunctions during aura were reported by one third of the patients in both groups (Table 2).

Also, there were no differences in demographic features, personal and family history nor characteristic of aura, between the groups of the patients with different grade of RLS, based on a 6-level logarithmic scale.

**Table 1**  
**Demographic features, personal and family history of migraine with aura (MA) patients with positive and negative transcranial Doppler (TCD) bubble-test**

Demographic features	MA patients with positive TCD bubble-test, n = 88	MA patients with negative TCD bubble-test, n = 47	<i>p</i> -value
Gender – female, n (%)	68 (77.3)	30 (63.8)	0.108
Actual age (years), $\bar{x} \pm SD$	33.6 $\pm$ 11.1	36.2 $\pm$ 14.6	0.241
Age at the onset of migraine (years), $\bar{x} \pm SD$	19.0 $\pm$ 8.3	20.9 $\pm$ 10.9	0.259
Migraine without aura in personal history, n (%)	22 (25.0)	13 (27.7)	0.837
Family history of migraine, n (%)	48 (54.5)	22 (46.8)	0.470
Family history of cerebrovascular disorders, n (%)	12 (13.6)	5 (10.6)	0.787

**Table 2**  
**Characteristics of aura in the migraine with aura (MA) patients with positive and negative transcranial Doppler (TCD) bubble-test**

Aura features	MA patients with positive TCD bubble-test, n = 88	MA patients with negative TCD bubble-test, n = 47	p-value
Duration (min), $\bar{x} \pm SD$	30.7 $\pm$ 18.6	28.9 $\pm$ 18.2	0.495
Somatosensory aura, n (%)	54 (61.4)	23 (48.9)	0.202
Visual aura, n (%)	80 (90.9)	44 (93.6)	0.747
Other cortical dysfunctions during aura, n (%)	25 (28.4)	17 (36.2)	0.435
Complex aura, n (%)	52 (59.1%)	25 (53.2)	0.585

## Discussion

In contrast to a large number of studies examining the potential causal relationship between MA and RLS, there is a few number of papers giving us data about the clinical characteristics of aura types in migraine patients with RLS<sup>17</sup>. The results of our study, completed on 135 patients, confirmed a high prevalence of RLS in the patients with MA, detected in 65.2% of our patients. The obtained results are in accordance with the results of the other authors<sup>1-4</sup>. In a line with results of these authors<sup>17</sup>, the significant difference of investigated demographic features of patients and clinical characteristics of aura between patients with and without RLS, was not found.

The proposed explanation of the comorbidity between MA and RLS is shared genetic inheritance<sup>18</sup>. According to the results of our study, migraine in the family history was equally present in the patients with and without RLS.

A substantial number of studies point to the increased risk of stroke in patients with MA compared to the patients

with migraine without aura<sup>19</sup>. The association between MA and RLS could contribute to this increased risk. The mechanism that underlies this association remains unclear, and according to the results of our study is not related to patient's demographic features or aura presentation.

## Conclusion

The results of our study confirm a high prevalence of right-to-left shunt in patients with migraine with aura, but the clinical relevance of this association has not been shown yet.

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