Are There Left–Right Differences in Ruptured Middle Cerebral Artery Bifurcation Aneurysms? A Single-Center Retrospective Study and Review of the Literature

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Introduction

Saccular aneurysms arising from the middle cerebral artery bifurcation (MCAB) are frequently encountered in our neurosurgical practice: ruptured MCAB aneurysms account for ~25 to 30% of aneurysmal subarachnoid hemorrhage (aSAH).

Background

The left (Lt) and right (Rt) middle cerebral artery bifurcation (MCAB) aneurysms have mostly been regarded as identical. Considering substantial Lt–Rt differences in hemispheric infarction, however, the presence of Lt–Rt differences may not be denied totally in patients with ruptured MCAB aneurysms. We herein investigated whether such Lt–Rt differences existed by a single-center retrospective study.

Materials and Methods

Clinical data prospectively acquired between 2011 and 2021 on 99 patients with ruptured MCAB aneurysms were analyzed. They were dichotomized based on the laterality, and demographic and outcome parameters were compared. Additionally, a literature review was conducted to elucidate possible Lt–Rt differences in the frequency of ruptured MCAB aneurysms (Rt/Lt ratio).

Results

Among the 99 patients, 42 had Lt and 57 had Rt ruptured MCAB aneurysms, with the Rt/Lt ratio of 1.36. Neither demographic, radiographic, nor outcome variables differed significantly between the two groups. A total of 19 studies providing information on the laterality of the ruptured MCAB were retrieved by literature search. A sum total for the Lt and Rt MCAB aneurysms was 671 and 940, making the Rt/Lt ratio of 1.40. After adding our data, a sum total for the Lt and Rt MCAB aneurysms was 713 and 997, making the Rt/Lt ratio of 1.40.

Conclusion

The Rt ruptured MCAB aneurysms were 1.40 times more frequent than the Lt-sided counterpart. While there may be some Lt–Rt differences in the MCA anatomy, it remains to be seen whether such anatomical differences are truly responsible for the disproportionately higher frequency of Rt MCAB aneurysms.
substantial Lt–Rt differences in patients with hemispheric or insular infarction, however, the presence of Lt–Rt differences cannot totally be denied in patients with ruptured MCAB aneurysms. We herein investigated whether such differences existed or not. In addition, a literature review was conducted to elucidate possible Lt–Rt differences in the frequency of ruptured MCAB aneurysms.

Materials and Methods
Study Population
This study used data from a total of 428 patients with aSAH admitted to our institution from January 2011 to December 2021. Among the 428 aSAH patients registered, there were 99 ruptured MCAB aneurysm patients (23%). They were dichotomized to the Lt (n = 42) versus Rt MCAB aneurysm (n = 57) groups. Therefore, the Rt/Lt ratio was 1.36. Demographic, clinical, radiographic, and outcome variables were compared between the two groups. Demographic variables compared included age, gender, proportion of severe SAH represented by the World Federation of Neurosurgical Societies (WFNS) grade IV/V SAH, presence of hypertension, diabetes mellitus, smoking, three familial connective tissue diseases known to be associated with brain aneurysm formation (Ehlers–Danlos’ syndrome, Marfan’s syndrome, and polycystic kidney diseases), and treatment modalities for the ruptured aneurysm (i.e., clipping vs. coiling). The frequency of those who had sustained symptomatic vasospasm was also compared. The patient outcomes were evaluated using a modified Rankin scale (mRS) score ≤2 at 3 months after aSAH onset.

Radiographic Measurement
An effort was made to elucidate possible Lt–Rt differences in the radiographic anatomy in the 99 ruptured MCAB aneurysm patients. Parameters measured included the diameter of the ruptured aneurysms, length of the M1 segment, aspect ratio, and presence of the mirror (contralateral) MCAB aneurysms measured using source images of the three-dimensional-computed tomography angiography in each patient.

Statistical Analysis
The Fisher’s exact test was used for categorical variables and unpaired t-test for continuous variables. JMP (SAS Institute, Cary, North Carolina, United States) was used for statistical analysis. Data are indicated by mean ± standard deviation, and p < 0.05 was considered statistically significant.

Literature Review
To evaluate possible differences in the Lt/Rt ratio, a review of the literature was conducted using internet databases PubMed, Scopus, and Google Scholar. The keywords for the literature search included ruptured, middle cerebral artery aneurysm, subarachnoid hemorrhage, Lt, and Rt. The literature published since 2001 with a sample size of >10 cases was searched extensively and reviewed rigorously. Literature in which no Lt–Rt distinction of MCAB aneurysms had been made was excluded from the analysis. Literature focusing solely on unruptured MCAB aneurysms was also excluded. Literature in which no distinction had been made between ruptured and unruptured MCAB aneurysms was analyzed separately.

Results
Demographic and Clinical Variables
The Lt MCAB aneurysm group (n = 42) consisted of 19 men and 23 women, with a mean age of 62.1 ± 13.5 years. The Rt MCAB aneurysm group (n = 57) consisted of 22 men and 35 women, with a mean age of 62.2 ± 11.5 years. Neither gender ratio nor age differed significantly between the two groups. The proportion of severe aSAH patients, represented by WFNS grade IV/V aSAH, was 57% in the Lt and 61% in the Rt MCAB aneurysm groups. The difference was not statistically significant (p = 0.68). There were no significant differences in the frequency of comorbid diseases (hypertension, diabetes mellitus, smoking, familial connective tissue diseases) between the two groups. There was no significant difference in the clipping versus coiling ratio. There was no significant difference in the frequency of those with symptomatic vasospasm (29 vs. 23%, p = 0.64). In addition, none of the radiographic parameters (aneurysm diameter, M1 length, aspect ratio, and frequency of mirror MCAB aneurysm) differed significantly between the two groups. The results of those two-group comparisons are shown in Table 1.

Outcomes
The frequency of favorable outcomes, represented as mRS score ≤2 at 3 months after aSAH onset, was compared after excluding 12 cases whose outcome data had been unavailable. The frequency was 47% in the Lt (n = 38) and 49% in the Rt (n = 49) MCAB aneurysm groups. The difference was not statistically significant (p = 1.00, Fig. 1).

Literature Review
A total of 19 studies that provided detailed information on the laterality of the ruptured MCAB aneurysms were retrieved following the literature search (Table 2). Each study is plotted in Fig. 1 based on its Rt/Lt ratio. In the great majority (17/19), the ratio exceeded 1.0. The sum total for the Lt and Rt MCAB aneurysms was 671 and 940, respectively, and therefore, the Rt/Lt ratio by the pooled literature analysis was 1.40 (Fig. 2). After adding our data, the sum total for the Lt and Rt MCAB aneurysms was 713 and 997, respectively, and therefore, the Rt/Lt ratio was 1.40 (Fig. 2).

Aside from the analysis described earlier focusing solely on the ruptured aneurysms, a total of seven studies that provided detailed information on the laterality of the MCAB aneurysms but failed to provide distinction between ruptured and unruptured status were retrieved following the literature search (Table 3). Each study is plotted in Fig. 2 based on its Rt/Lt ratio. In all studies (7/7), the
neurosurgeons have not paid much attention to thisLt difference in the MCAB aneurysms. Nevertheless, consider-
and 49% in the Rt (MCAB, middle cerebral artery bifurcation; Rt, right).

The frequency of favorable outcomes (mRS ≤ 2 at 3 months after aSAH onset) was compared after excluding 12 patients whose data had been unavailable. The frequency was 47% in the Lt (n = 38) and 49% in the Rt (n = 49) MCAB aneurysm groups. The difference was not statistically significant. aSAH, aneurysmal subarachnoid hemorrhage; MCAB, middle cerebral artery bifurcation; Rt, right.

**Discussion**

Unlike patients with hemispheric or insular ischemic stroke,3–6 no significant Lt–Rt differences in demographic and outcome variables were found in our cohort of ruptured MCAB aneurysm patients. The lack of difference in the out-
combs, evaluated with the mRS scores mainly focusing on the ability to walk independently, is compatible with the results of previous studies,2,23 and it is understandable why many neurosurgeons have not paid much attention to this Lt–Rt difference in the MCAB aneurysms. Nevertheless, considering the proximity of Broca’s area and Lt MCA, it is not surprising that patients with ruptured MCA aneurysms fared worse in the recovery of postoperative language functions.33 Therefore, the presence of the Lt–Rt difference in ruptured MCAB patients may not completely be excluded, particularly in the domain of cortical higher functions. Continued efforts to investigate this issue may not be futile.

Regarding the Lt/Rt ratio of ruptured MCAB aneurysms, there was striking concordance between the analysis on literature and the analysis on our cohort, pointing the Lt/Rt ratio of 1.40 (Fig. 2). In addition, the Lt/Rt ratio was also 1.40 in a separate analysis on studies without distinction between ruptured and unruptured MCAB aneurysms (Fig. 3).26–32 Although we made the separate analysis fearing for possible inhomogeneity between ruptured and unruptured aneurysm patients (Fig. 3, Table 3), the results might virtually be identical. Interestingly, the Lt/Rt ratios were comparable among the Asian and Caucasian populations (Tables 2 and 3), indicating that the ratio may not be affected by ethnicity. This is probably the first study to report on the marked Lt–Rt difference regarding the frequency of ruptured MCAB aneurysms. While the reason why the Rt MCAB aneurysms develop more frequently than the Lt MCAB aneurysms remains unclear, the Lt–Rt difference in the MCA anatomy may possibly be involved. Recently, da Cunha and da Cunha Correia reported that those with an MCAB aneurysm had signi-
fied here as those with a history of Ehlers–Danlos’ syndrome, Marfan’s syndrome, and polycystic kidney diseases, all known to be associated with brain aneurysm formation.

**Table 1** Comparison of demographic variables between Lt and Rt ruptured MCAB aneurysms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lt MCAB (n = 42)</th>
<th>Rt MCAB (n = 57)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>62.1 ± 13.5</td>
<td>62.2 ± 11.5</td>
<td>0.99</td>
</tr>
<tr>
<td>Male:female</td>
<td>19:23</td>
<td>22:35</td>
<td>0.54</td>
</tr>
<tr>
<td>Severe SAH (WFNS grade IV/V)</td>
<td>24 (57%)</td>
<td>35 (61%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (52%)</td>
<td>28 (49%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (7%)</td>
<td>5 (9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 (36%)</td>
<td>26 (46%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Familial connective tissue diseasesa</td>
<td>2 (5%)</td>
<td>2 (4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Clipping vs. coilingb</td>
<td>36:1</td>
<td>48:1</td>
<td>1.00</td>
</tr>
<tr>
<td>Symptomatic vasospasm</td>
<td>12 (29%)</td>
<td>13 (23%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Mean aneurysm diameter (mm)</td>
<td>6.5 ± 4.3</td>
<td>7.1 ± 5.4</td>
<td>0.59</td>
</tr>
<tr>
<td>M1 segment length (mm, ruptured side)</td>
<td>183 ± 53</td>
<td>174 ± 46</td>
<td>0.53</td>
</tr>
<tr>
<td>Aspect ratio</td>
<td>1.69 ± 0.56</td>
<td>1.76 ± 0.58</td>
<td>0.58</td>
</tr>
<tr>
<td>Mirror (contralateral MCAB) aneurysm</td>
<td>4 (10%)</td>
<td>4 (7%)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Abbreviations: Lt, left; MCAB, middle cerebral artery bifurcation; Rt, right; SAH, subarachnoid hemorrhage; WFNS, World Federation of Neurosurgical Societies.

aConnective tissue diseases: defined here as those with a history of Ehlers–Danlos’ syndrome, Marfan’s syndrome, and polycystic kidney diseases, all known to be associated with brain aneurysm formation.
bClipping versus coiling: 12 patients treated conservatively had been excluded.
Table 2 Published articles describing Lt/Rt ratio of MCAB aneurysms (ruptured only)

<table>
<thead>
<tr>
<th>No.</th>
<th>Authors (Ref. no.)</th>
<th>Journal, publication year</th>
<th>N</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lee et al 16</td>
<td>J Korean Neurosurg Soc 2001</td>
<td>134</td>
<td>1:1.44</td>
</tr>
<tr>
<td>2</td>
<td>Choi et al 19</td>
<td>J Korean Neurosurg Soc 2004</td>
<td>85</td>
<td>1:1.56</td>
</tr>
<tr>
<td>4</td>
<td>Mutoh et al 20</td>
<td>Neurol Med Chir (Tokyo) 2010</td>
<td>26</td>
<td>1:1.60</td>
</tr>
<tr>
<td>5</td>
<td>Kazumata et al 14</td>
<td>Neurol Med Chir (Tokyo) 2010</td>
<td>23</td>
<td>1:0.92</td>
</tr>
<tr>
<td>6</td>
<td>Lee et al 15</td>
<td>J Cerebrovasc Endovasc Neurosurg 2012</td>
<td>24</td>
<td>1:1.67</td>
</tr>
<tr>
<td>7</td>
<td>Lin et al 18</td>
<td>J Neurosurg 2012</td>
<td>40</td>
<td>1:1.26</td>
</tr>
<tr>
<td>8</td>
<td>Elsharkawy et al 12</td>
<td>Neurosurgery 2013</td>
<td>407</td>
<td>1:1.41</td>
</tr>
<tr>
<td>9</td>
<td>Inamasu et al 1</td>
<td>Stroke 2013</td>
<td>79</td>
<td>1:1.47</td>
</tr>
<tr>
<td>10</td>
<td>Bohnstedt et al 8</td>
<td>World Neurosurg 2013</td>
<td>116</td>
<td>1:1.15</td>
</tr>
<tr>
<td>11</td>
<td>Zhang et al 24</td>
<td>World Neurosurg 2017</td>
<td>30</td>
<td>1:1.14</td>
</tr>
<tr>
<td>12</td>
<td>Zijlstra et al 25</td>
<td>Neuroradiology 2018</td>
<td>76</td>
<td>1:1.17</td>
</tr>
<tr>
<td>13</td>
<td>Mooney et al 19</td>
<td>J Neurosurg 2018</td>
<td>46</td>
<td>1:1.56</td>
</tr>
<tr>
<td>14</td>
<td>Hoz et al 13</td>
<td>Roman Neurosurg 2020</td>
<td>47</td>
<td>1:1.94</td>
</tr>
<tr>
<td>15</td>
<td>Xue et al 23</td>
<td>Front Neurol 2021</td>
<td>40</td>
<td>1:1.50</td>
</tr>
<tr>
<td>16</td>
<td>Darsaut et al 10</td>
<td>World Neurosurg 2021</td>
<td>71</td>
<td>1:1.37</td>
</tr>
<tr>
<td>17</td>
<td>Dallaretti et al 11</td>
<td>Interdiscip Neurosurg 2021</td>
<td>113</td>
<td>1:1.05</td>
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<tr>
<td>18</td>
<td>Sturiale et al 22</td>
<td>Neurosurg Rev 2022</td>
<td>163</td>
<td>1:1.51</td>
</tr>
<tr>
<td>19</td>
<td>Li et al 17</td>
<td>Front Surg 2022</td>
<td>80</td>
<td>1:2.08</td>
</tr>
</tbody>
</table>

Subtotal: 1,611, Ratio: 1:1.40

Our study: 99, Ratio: 1:1.36

Total: 1,710, Ratio: 1:1.40

Abbreviations: Lt, left; MCAB, middle cerebral artery bifurcation; Rt, right.

Fig. 2 A total of 19 studies providing detailed information on the side of the ruptured MCAB aneurysms were retrieved. Each study was plotted based on its Rt/Lt ratio. The sum total for the Lt and Rt MCAB aneurysms pooled from literature was 671 and 940, with the Rt/Lt ratio of 1.40 (subtotal). After adding our study with the Rt/Lt ratio of 1.36, the sum total for the Lt and Rt MCAB aneurysms was 713 and 997, with the Rt/Lt ratio of 1.40 (total). Lt, left; MCAB, middle cerebral artery bifurcation; Rt, right.
difference in the length of M1 segment in our cohort (Table 1), however, and it remains unclear or questionable whether the Lt–Rt difference in the length of M1 segment truly explain the substantial Lt–Rt difference in the frequency of MCAB aneurysms. There may also seem to be a possible Lt–Rt difference in the MCAB angle, which is a known risk factor for aneurysm formation.41,42 The Rt MCAB angle was shown to be larger than the Lt MCAB angle in several studies,41,43,44 although the difference was nonsignificant. It remains to be seen in future studies whether those differences in the MCA anatomy could explain the higher frequency of the Rt MCAB aneurysms.45

There are several limitations in this study. First, the outcomes were evaluated only at hospital discharge. Difference might have become more apparent with longer observation period. Second, while we made every effort to retrieve as many articles as possible to make the literature review comprehensive, the review was not systematically conducted and might be affected by selection bias. Therefore, we are currently collecting resources for conducting systematic review on this issue. Third, we intentionally excluded unruptured MCAB aneurysms in this analysis, because of possible mismatch between number of patients and number of aneurysms which are often multiple.

**Conclusion**

The Rt ruptured MCAB aneurysms were 1.40 times more frequent than the Lt-sided counterpart. While there may be some Lt–Rt differences in the MCA anatomy, it remains to be seen whether such anatomical differences are truly responsible for the disproportionately higher frequency of Rt MCAB aneurysms. While the difference is unlikely to have great impact on our daily practice, a knowledge that the Lt MCAB and Rt MCAB aneurysms may not entirely be identical may lead to another finding which may have been unnoticed.
Authors’ Contributions
Joji Inamasu contributed to writing and data collection. Katsuya Saito contributed to data collection and supervision.

Availability of Data and Material
Raw data were generated at our institution. Derived data supporting the findings of this study are available from the corresponding author (J.I.) on request.

Ethical Approval
This study was approved by our institutional ethics committee (authorization no. 17-012). And conducted in accordance with the Declaration of Helsinki. The need for informed consent from each participant was waived by the ethical committee.

Funding
None.

Conflict of Interest
None declared.

References


Baharoglu MI, Lauric A, Safain MG, Hippelheuser J, Wu C, Malek AM. Widening and high inclination of the middle cerebral artery bifurcation are associated with presence of aneurysms. Stroke 2014;45(09):2649–2655
