A small percentage of patients with intracranial aneurysms will develop a second, new aneurysm, anatomically unrelated to their initial lesion. These aneurysms are termed "de novo." By definition, a de novo aneurysm is a lesion that develops from a vessel that had been normal on previous imaging studies.

A number of published studies have estimated the risk of forming a de novo aneurysm to range between 0.37% and 4.15% per year after discovery of an original aneurysm. Previous studies have consistently identified female sex, history of hypertension, and smoking as risk factors for de novo aneurysm formation.

Although there are reports estimating the incidence of formation of de novo aneurysms, there is very little published data studying the clinical behavior of these lesions. A fundamental question is whether these aneurysms have a similar natural history to an unruptured intracranially discovered aneurysm. Our goal is to estimate the cumulative risk and risk factors for hemorrhage from these lesions in this cohort study of 37 patients.

**Methods**

The Goodman Campbell Brain and Spine neurosurgery practice in Indianapolis, Indiana, has prospectively...
De novo intracranial aneurysms

maintained a database of all patients diagnosed with cerebral aneurysms since 1976. A retrospective review of this prospectively collected data was performed. Supplemental information was obtained from patient charts, operative notes, and radiological reports. The study began after approval from the institutional review board of Methodist Hospital, Indiana.

The database included 4718 patients with intracranial aneurysms evaluated from January 1976 through December 2010. All cases involving the discovery of a true de novo aneurysm were evaluated. We identified 27 patients with de novo aneurysms identified on routine follow-up imaging. We identified another 10 patients who suffered an SAH from a de novo aneurysm after treatment of their original aneurysm. We excluded 3 patients who had aneurysms associated with arteriovenous malformations and those with recurrence of an aneurysm at the original site. We reviewed the initial imaging studies to ensure that the de novo aneurysm had formed in an anatomical area that was previously visualized as normal. Patients with inadequate initial studies of the anatomy were excluded. We tabulated characteristics and presumed risk factors for the 37 included patients.

Our general policy is to perform a formal angiogram in the immediate postoperative period after clip ligation or coil embolization of an aneurysm. This may include a satisfactory intraoperative study. The subsequent follow-up imaging is dependent on the patient’s clinical status, treatment, surgeon preference, and patient preference. In this study, we focused on patients with follow-up imaging beyond the perioperative period.

We evaluated each aneurysm separately. There were 42 de novo aneurysms in the 37 patients. We evaluated these aneurysms for size, location, and hemorrhage. We formed 2 groups for statistical analysis: de novo aneurysms that bled (10 lesions) and de novo aneurysms that did not bleed (32 lesions). We performed multivariate statistical analysis comparing the groups to identify any risk factors for hemorrhage. We calculated the risk of hemorrhage by taking the total number of patient years in follow-up divided by the number of hemorrhages.

Statistical analysis was performed using Minitab (version 14.2) software. The Student t-test and Fisher exact test were used to compare variables between the group that hemorrhaged and the one that did not. Risk factors studied included patient age, use of tobacco products, use of alcoholic beverages, family history, sex, history of previous aneurysm rupture, anatomical location of the de novo aneurysm, and patient comorbidities (hypertension, cardiovascular disease, renal disease, history of polycystic kidney or ovarian disease, and diabetes). The risk factors were based on the history and physical examination at presentation of the initial aneurysm. Statistical significance was set at p = 0.05.

Results

De Novo Aneurysm Patient Population

We identified 611 (13.0%) of the 4718 patients as having adequate follow-up imaging studies beyond the initial perioperative period. Of these 611 patients, we identified 27 (4.4%) in whom a total of 32 de novo aneurysms were identified on routine surveillance imaging. We identified another 10 patients who presented with SAH from ruptured de novo aneurysms. All of these 10 patients had their original aneurysm treated by our group; the new hemorrhage was confirmed to be from a new (de novo) aneurysm. The demographics and characteristics of these 37 patients are shown in Table 1.

There was a strong gender bias. Thirty-two (86.5%) of the 37 patients were female. Thirty-two (86.5%) were smokers. Fourteen (37.8%) had a history of hypertension. The mean age at diagnosis of the de novo aneurysm was 50.3 years (range 34–83 years). Eighteen patients (48.6%) presented originally with SAH from their initial aneurysm. Seven (18.9%) had multiple aneurysms on initial presentation.

Risk Factors for Hemorrhage of De Novo Aneurysms

We identified 42 de novo aneurysms in the 37 patients. We analyzed these aneurysms individually for location, size, and hemorrhage.

Ten (23.8%) of the 42 aneurysms bled. There was a total of 347.1 years of imaging follow-up. This leads to an estimated risk of hemorrhage of 2.9% per year.

The 10 aneurysms that bled were compared with the 32 that did not bleed. The comparison between these 2 groups is shown in Table 2. Patient age for the aneurysms that bled was significantly older than for those that did not bleed (mean [SD] 57.7 ± 14.7 years vs 49.5 ± 9.7, p = 0.047). There was also a significant between-groups difference in the length of time between treatment of the initial aneurysm and the discovery of the de novo aneurysm (12.0 ± 6.5 years in the group that hemorrhaged com-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>32 (86.5)</td>
</tr>
<tr>
<td>male</td>
<td>5 (13.5)</td>
</tr>
<tr>
<td>multiple aneurysms at initial presentation</td>
<td>7 (18.9)</td>
</tr>
<tr>
<td>SAH w/ original aneurysm</td>
<td>18 (48.6)</td>
</tr>
<tr>
<td>age at Dx of de novo aneurysm (yrs)</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>50.3 ± 11.7</td>
</tr>
<tr>
<td>range</td>
<td>34–83</td>
</tr>
<tr>
<td>risk factors</td>
<td></td>
</tr>
<tr>
<td>smoker</td>
<td>32 (86.5)</td>
</tr>
<tr>
<td>history of hypertension</td>
<td>14 (37.8)</td>
</tr>
<tr>
<td>history of CVD</td>
<td>7 (18.9)</td>
</tr>
<tr>
<td>family history of aneurysm</td>
<td>6 (16.2)</td>
</tr>
<tr>
<td>history of drug abuse</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>history of head injury/trauma</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>alcohol use (&gt;1 drink per day)</td>
<td>14 (37.8)</td>
</tr>
</tbody>
</table>

* Values represent numbers of patients (%) unless otherwise indicated. The mean value is given with the SD. Abbreviations: CVD = cardiovascular disease; Dx = diagnosis.
pared with 7.1 ± 5.3, p = 0.020). There was no statistically significant difference in the risk factors of hypertension, diabetes, alcohol use, smoking, polycystic kidney disease, cardiovascular disease, family history, or history of prior SAH. The difference with respect to drug abuse trended toward significance; however, the small numbers in each group preclude definite conclusions. There was also no statistically significant difference in aneurysm location (anterior versus posterior circulation). Note that all de novo aneurysms in this series were “small” (< 10 mm).

### Discussion

The first description of a “de novo” aneurysm was published by Graf and Hamby. 12 Multiple case reports and small series have been documented since. 2,6,9,10,14,17,18,20–23,25–27,29,31–33 The findings support the concept that the process of aneurysm formation is multifactorial and related to congenital, environmental, and hemodynamic factors.4,5,8,35

There are consistently reported risk factors for the development of de novo aneurysms. Similar to previous publications, our series shows a predominance of females and smokers.16,37 While only 37.8% of our patients had hypertension, previous series have shown a high rate of hypertension in patients with de novo aneurysms.1,33,37,41 De novo aneurysms have been well documented after carotid artery occlusion, presumably because of a shift in the blood flow pattern.11,13,19,36,39,40,43 Other risk factors noted included history of radiation exposure,30 familial aneurysms,15,21 and multiple aneurysms on initial diagnosis.3,7

A number of previously published studies have estimated the risk of de novo aneurysm formation to be 0.37%–4.15% per year.7,16,25,38,41 Juvela et al.16 studied 87 aneurysm patients for a mean follow-up of 18.9 ± 9.4 years. Fifteen patients developed 19 de novo aneurysms over 1789 follow-up patient-years; the calculated probability of de novo aneurysm formation was 0.84% per year. Wermer et al.41 screened 610 patients with CT angiography. They identified 19 true de novo aneurysms with a calculated incidence of 0.37%–1.2% per year. Tsutsumi et al.38 calculated the risk of de novo aneurysm formation to be 0.89% per year in a study of 112 patients undergoing angiographic follow-up at a mean interval of 9.3 years after aneurysm surgery. David et al.7 calculated the annual risk of de novo aneurysm formation to be 1.8% per year in 102 patients with a mean follow-up interval of 4.4 ± 1.6 years after their original surgery. Miller et al.25 estimated a risk of 60/100,000 per year of formation and rupture of a de novo aneurysm. This was based on 6 patients with de novo aneurysm hemorrhage out of 620 consecutively treated aneurysm patients. In a more recent study, Brueneau et al.3 reported on patients undergoing angiography more than 10 years after previous treatment for a ruptured aneurysm. They found a higher rate of “up to 30%” new aneurysms. Their calculated rate of de novo aneurysm formation was 4.15% per year.

While these papers consistently demonstrate a low rate of formation of de novo aneurysms, they rarely address the subsequent clinical behavior of these lesions. An unanswered clinical question is whether the behavior of a de novo aneurysm is similar to that of an initially discovered saccular aneurysm. An incidentally discovered small aneurysm has a very low risk of hemorrhage. The ISUIA trial42 prospectively showed a 5-year cumulative risk of hemorrhage from small (< 7 mm), unruptured anterior circulation aneurysms of 0% for patients with no previous SAH and 1.5% for patients with a history

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**TABLE 2: Statistical tabulation of 42 de novo aneurysms (in 37 patients) stratified by presence of SAH: comparison of patient and aneurysm characteristics in the 2 groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No SAH (32 aneurysms)</th>
<th>SAH (10 aneurysms)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean age (yrs)</td>
<td>49.5 ± 9.7</td>
<td>57.7 ± 14.7</td>
<td>0.047</td>
</tr>
<tr>
<td>female sex</td>
<td>28 (87.5)</td>
<td>9 (90.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>prior SAH</td>
<td>18 (56.3)</td>
<td>8 (80.0)</td>
<td>0.270</td>
</tr>
<tr>
<td>mean time from Tx of initial aneurysm (yrs)</td>
<td>7.1 ± 5.3</td>
<td>12.0 ± 6.5</td>
<td>0.020</td>
</tr>
<tr>
<td><strong>risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypertension</td>
<td>12 (37.5)</td>
<td>4 (40.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>diabetes</td>
<td>0</td>
<td>1 (10.0)</td>
<td>0.238</td>
</tr>
<tr>
<td>alcohol use</td>
<td>12 (37.5)</td>
<td>2 (20.0)</td>
<td>0.451</td>
</tr>
<tr>
<td>tobacco use</td>
<td>28 (87.5)</td>
<td>8 (80.0)</td>
<td>0.616</td>
</tr>
<tr>
<td>drug abuse</td>
<td>0</td>
<td>2 (20.0)</td>
<td>0.052</td>
</tr>
<tr>
<td>PKD</td>
<td>3 (9.4)</td>
<td>2 (20.0)</td>
<td>0.537</td>
</tr>
<tr>
<td>CVD</td>
<td>7 (21.9)</td>
<td>2 (20.0)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>de novo aneurysm characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>size</td>
<td>3.9 ± 1.9</td>
<td>4.7 ± 2.4</td>
<td>0.426</td>
</tr>
<tr>
<td>anterior circulation</td>
<td>18 (56.3)</td>
<td>6 (60.0)</td>
<td></td>
</tr>
<tr>
<td>posterior circulation</td>
<td>14 (43.8)</td>
<td>4 (40.0)</td>
<td></td>
</tr>
</tbody>
</table>

* PKD = polycystic kidney disease; Tx = treatment.
De novo intracranial aneurysms

of SAH. There was also a low risk of hemorrhage from small, posterior communicating artery or posterior circulation aneurysms (2.5% in patients with no history of SAH and 3.4% in patients with a history of SAH).

There is very little published data studying the natural history and risk of hemorrhage of de novo aneurysms. Previous studies involve small numbers and often do not include unruptured de novo aneurysms. In this paper, we do not attempt to calculate the risk of formation of these aneurysms. Our goal in this paper was to evaluate the risk of hemorrhage once a de novo aneurysm is discovered. In our series, all 42 de novo aneurysms were smaller than 7 mm in maximum diameter. There was a total of 347.1 years of patient follow-up. In our study, the calculated risk of hemorrhage from de novo aneurysm was 2.9% per year and 14.5% over 5 years. This is higher than the risk for similar-size aneurysms reported in the ISUIA trial.

Thirty-two de novo aneurysms were discovered in 27 patients on routine follow-up screening. We compared these to the 10 aneurysms discovered after hemorrhage. In a statistical comparison between the 2 groups, we did not find a significant risk difference between anterior and posterior circulation aneurysms. There was no statistically significant between-groups difference with respect to the risk factors of sex, hypertension, or smoking. Note that both groups had a high percentage of females and smokers, accepted risk factors for the formation of de novo aneurysms.

The timing of formation and hemorrhage from a de novo aneurysm varies. Previously published case reports suggest a high rate of SAH in rapidly developing de novo aneurysms, especially in hypertensive patients.24,28,34,37,44 However, other reports suggest a longer time between discovery of the initial aneurysm and discovery of the de novo aneurysm. Yoneoka et al.45 reported on 12 patients with ruptured de novo aneurysms. These patients presented 6.39–15.1 years after treatment of their initial aneurysm. In our series, the group with SAH from a de novo aneurysm was statistically significantly older than the non-SAH group (p = 0.047). This could be interpreted as age being a risk factor for hemorrhage; however, it could also be interpreted as a continued cumulative risk over a longer follow-up time. Indeed, the interval between the treatment of the initial aneurysm and the discovery of the de novo aneurysm was statistically significantly longer in the SAH group than in the non-SAH group (12.0 ± 6.5 vs 6.8 ± 5.0 years, p = 0.011). Our data suggests that this risk of hemorrhage is cumulative. We therefore feel that long-term follow-up is warranted.

Study Limitations

While our series has a larger population of patients with de novo aneurysms than any previously published study, the relatively small numbers preclude definitive conclusions. The biggest weakness in our data is the lack of consistent follow-up. Imaging studies after the immediate postoperative period were rare in the early years of our database. This is likely due to the reluctance to order an angiogram after the patient is presumed “cured.” We found surprisingly few previously published long-term angiographic studies following successful clip ligation of aneurysms, probably due to the low risk of future hemorrhage, cost, and small but unavoidable risk of complications with invasive tests. With the advent of noninvasive imaging studies and the recognized need for close follow-up of coiled aneurysms, we believe more data will be available in the future.

We did not feel our data were sufficient to calculate a risk of formation of de novo aneurysms. With a lack of standardized follow-up, there may be patients with undiscovered, unruptured de novo aneurysms. This may skew the calculations of the risk of hemorrhage. Therefore, our risk numbers should be considered estimates only.

Conclusions

De novo aneurysms may form after successful treatment of a prior aneurysm. We agree with other authors who suggest the need for long-term surveillance for all aneurysm patients. In our calculations, the 5-year cumulative risk of hemorrhage of a small de novo aneurysm was 14.5%, more than 4 times the highest risk group of small aneurysms in the ISUIA trial. Our data suggest the possibility that a de novo aneurysm has a higher risk of hemorrhage than an incidentally discovered initial aneurysm of comparable size. Given the limitations in our data and the rarity of the lesions, we suggest that a multicenter, prospective study is warranted to fully answer this question.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Fulkerson, Kemp, Cohen-Gadol. Acquisition of data: Kemp, Palmer. Analysis and interpretation of data: Fulkerson, Kemp, Payner, Leipzig, Cohen-Gadol. Drafting the article: Fulkerson, Kemp. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fulkerson. Administrative/technical/material support: Palmer. Study supervision: Fulkerson.

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