Understanding Rupture Risk Factors for Intracranial Aneurysms: Which Ticking Time Bomb Needs to Be Defused?

Understanding the natural history of a disease is paramount to defining treatment strategies and algorithms. Intracranial aneurysms are no exception to this rule. Over the past decade, an extensive body of literature has been generated with the goal of improving our understanding of intracranial aneurysms and the factors that govern their natural history. In particular, the authors recommended observation for aneurysms <5 mm and treatment for aneurysms >10 mm. For aneurysms between 5 and 10 mm, risks of treatment vs observation were discussed with the patients. Patients were followed up until time of subarachnoid hemorrhage (SAH), death resulting from any cause, or last possible follow-up contact. Patients were divided into 2 groups. Group 1 was composed of patients with no history of SAH, and group 2 was composed of patients with a history of SAH. Patients who presented with signs and symptoms of mass effect were treated urgently. Mean follow-up was 7388 aneurysm-years. The most common was middle cerebral artery (MCA) aneurysms (535 aneurysms, 27.3%), followed by internal carotid artery (ICA) aneurysms not connected to the origin of the posterior communicating artery (PCom; 525 aneurysms, 26.8%). Aneurysms at the origin of the PCom were the third most common (401 aneurysms, 20.5%), followed by vertebral–basilar artery aneurysms (169 aneurysms, 8.6%). Fifty-six aneurysms ruptured during the follow-up period, with an overall annual incidence SAH of 0.76%. Mean duration to rupture from initial presentation was 547 days. Regarding the rupture risk factors, aneurysm size, specific location, history of SAH, and the presence of a daughter sac were found to be independent risk factors in both single and multivariate Cox proportional-hazard models. On the other hand, and surprisingly, smoking, family history of SAH, age, female sex, hypertension, and diabetes mellitus were not associated with risk of rupture. Average rupture size was 7.5 ± 5.74 mm. Of note, 39 ruptures (69.6%) occurred in aneurysms <7 mm in size. The probability of rupture increased with size. The authors then performed multiple analyses with the cutoff size set at 5, 6, 7, 8, 9, and 10 mm. They noted a statistical significance in all selected cutoff sizes with and without adjustment for other risk factors. In terms of locations (Table), vertebrobasilar aneurysms were associated with the highest rupture risk, followed by PCom, MCA, anterior cerebral artery (ACA), and then finally ICA aneurysms. Vertebrobasilar and PCom aneurysms had a significantly higher hazard ratio of rupture, whereas MCA and ACA aneurysms had only a moderate increase in risk. Fifteen of the 56 aneurysm ruptures (26.8%) resulted in death, and 16 of the 56 (28.6%) ended in moderate to severe disability (modified Rankin Scale score of 3–5). Fewer than half of the patients with ruptures returned to normal life. None of the patients who had large or giant aneurysms recovered without deficits. The mortality rate of these patients was 69% (9 of 13), whereas the mortality rate of aneurysms <5 mm was 18% (4 of 22).

This study confirms many concepts about intracranial aneurysms. More than half of the ruptured aneurysms ended in at least moderate disability, further revealing the devastating effect of aneurysmal SAH. Size and location have again been shown to be independent risk factors for rupture. Unlike ISUIA, however, this study

Table: Annual Rate of Rupture According to Size and Location of Aneurysm

<table>
<thead>
<tr>
<th>Location</th>
<th>2-4 mm</th>
<th>5-6 mm</th>
<th>7-9 mm</th>
<th>10-24 mm</th>
<th>≥25 mm</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA</td>
<td>0.45 (0.19-1.07)</td>
<td>1.37 (0.57-3.31)</td>
<td>2.6 (0.27-26.2)</td>
<td>0.72 (0.37-1.38)</td>
<td>0.2 (0.08-0.55)</td>
<td></td>
</tr>
<tr>
<td>ICA without Pcom</td>
<td>0.11 (0.28-0.45)</td>
<td>0.47 (0.66-33.2)</td>
<td>2.6 (0.37-18.6)</td>
<td>0.2 (0.08-0.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA-Pcom</td>
<td>0.29 (0.11-0.77)</td>
<td>3.78 (1.22-11.73)</td>
<td>8.38 (2.70-25.97)</td>
<td>31.98 (13.27-76.60)</td>
<td>220.03 (30.99-1562.81)</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>0.44 (0.22-0.87)</td>
<td>3.0 (1.20-7.20)</td>
<td>0.30 (0.05-3.0)</td>
<td>0.79 (0.48-1.28)</td>
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<tr>
<td>VABA</td>
<td>0.62 (0.20-1.91)</td>
<td>6.43 (2.67-15.44)</td>
<td>8.6 (1.47-23.52)</td>
<td>2435 (343-17286.24)</td>
<td></td>
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<tr>
<td>Overall aneurysm-years</td>
<td>0.33 (0.22-0.51)</td>
<td>3.07 (1.91-4.93)</td>
<td>2.9 (1.09-7.72)</td>
<td>10.24 (5.67-18.49)</td>
<td>33.05 (8.27-132.17)</td>
<td></td>
</tr>
</tbody>
</table>

showed what was suspected all along: that even small aneurysms rupture. Although the authors are to be commended for their efforts, this study has obvious limitations. First, there is a clear selection bias. Aneurysms suspected to be of high risk of rupture were treated outside of this cohort, which would explain the low incidence of SAH in their population. These include irregular aneurysms and aneurysms that presented with mass effect. In terms of risk factors, some findings replicated what has been previously published in the literature (eg, size, location, daughter sac, and history of SAH). Other conclusions failed to corroborate findings from other studies (eg, smoking, hypertension). Although this could be due to selection bias or small population size, it could also be explained by the variability in aneurysm natural history and further highlights our lack of understanding of the pathology.

Although statistics generated by large-scale studies help us to better understand diseases, it should be noted that they apply for the general masses and give a global perspective and therefore have little implication for an individual in the clinic. This is particularly an issue when the number of variables increases such as in the case of aneurysms. As an example, a patient with a connective tissue disease with a 5-mm ACA aneurysm might be at a higher risk than an otherwise healthy patient with a 9-mm MCA aneurysm. When other variables such as age, aneurysm growth, shape, smoking, and SAH history are factored in, the complexity increases exponentially. In addition, aneurysm formation risk factors are not necessarily the same as rupture risk factors. In an ideal world, mathematically generated individualized risk assessment models would assist in decision-making and treatment algorithms. At this point in time, however, such a model remains out of immediate and practical reach. Further studies are required to improve our understanding of aneurysms on multiple levels, including clinical, biological, and mechanical.

Rudy J. Rahme, MD*  
Andrew R. Pines, MA‡  
Chandan Krishna, MD‡  
Bernard R. Bendok, MD, MSCI‡  
*Department of Neurological Surgery  
Northwestern Memorial Hospital and  
McGaw Medical Center  
Chicago, Illinois  
‡Department of Neurological Surgery  
Mayo Clinic, Phoenix, Arizona  

REFERENCES  

Transdifferentiation-Induced Neural Stem Cells for the Treatment of Malignant Gliomas

Glioblastoma (GBM) remains the deadliest malignant primary brain tumor, with >12 000 new patients diagnosed yearly and a median life expectancy of approximately 16 months despite maximal multimodal treatments. There has recently been an increasing interest in personalized medicine in tailoring treatments for many forms of cancers, including GBM. Cellular reprogramming techniques have been developed that may allow the development of large numbers of personalized stem cells. Transdifferentiation is such a technique that reprograms somatic stem cells into another cell type by bypassing dedifferentiation into a pluripotent state. Transdifferentiation can be used to create induced neural stem cells (iNSCs). Previous in vivo research using induced pluripotent stem cells has been stymied by the formation of cancerous teratomas. However, iNSCs have not shown such in vivo teratoma formation, suggesting that iNSCs can provide safe, patient-specific cell transplantation therapy to treat disorders of the central nervous system.1,2

NSCs exhibit tumorigenic migration, allowing unprecedented access to GBM cancer cells. NSCs also have the ability to release anticancer molecules that could provide long-term drug delivery directly to the cancer cells.3 However, NSCs are located deep within the adult brain and are not readily available without invasive surgery. A recent study by Bagó et al4 shows a potential means of inducing NSCs from skin fibroblasts and specifically delivering tumoricidal treatments to GBM in vivo.

The investigators generated iNSCs from mouse embryonic fibroblasts by transducing them with lentiviral vectors encoding transcription factors Brn2, Sox2, and FoxG1. The iNSCs were also designed to express a secreted variant of the proapoptotic molecule tumor necrosis factor–α–related apoptosis-inducing ligand (TRAIL). The iNSCs were shown to retain their ability to proliferate and differentiate. The investigators then cocultured the iNSCs with GBM cells in vitro and tracked them with optical reporters (Figure). Time-lapse imaging then showed that iNSCs were tumoritropic, readily homing to the cocultured GBM cells. They secreted TRAIL proteins, killing GBM cells in culture. When implanted into mice brains with GBM xenografts, they suppressed tumor growth and significantly extended survival. These results held when iNSCs were implanted into the contralateral hemisphere from GBM xenografts. Postmortem analyses showed that iNSCs had migrated into the contralateral hemisphere to attack GBM cells. The authors concluded that these data support the potential of iNSCs to serve as effective drug-delivery vehicles for the treatment of solid and invasive brain tumors.

The study by Bagó et al is extremely promising. The use of iNSCs could potentially lead to highly selective delivery of therapeutics to brain tumors, reducing systemic toxicities and improving