DIAGNOSTIC AND THERAPEUTIC DILEMMAS IN THE MANAGEMENT OF INTRACRANIAL ANEURYSMS

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SUMMARY – Intracranial aneurysms have a prevalence of about 2% of the population. They are a common incidental finding of noninvasive neuroimaging methods, raising the question of the necessity of treatment of patients with an asymptomatic intracranial aneurysm. For long, the only treatment option was surgical clipping of aneurysm neck. In the last 25 years, endovascular techniques have been developed as an alternative solution for patients who are not eligible for neurosurgical procedures. Research has shown better results of embolization procedures with lower rates of complications, but a higher rate of recanalization is still a major drawback of endovascular coiling. There are no strict protocols and the treatment of choice for intracranial aneurysms should be agreed upon by both the physician and the patient. This review aims to provide an insight into the management of intracerebral aneurysms with emphasis on the decision making problems faced by clinicians.

Key words: Intracranial aneurysm; Embolization; Clipping; Treatment

Introduction

Intracranial aneurysms are local dilatations of cerebral arteries that most commonly appear in a saccular form (berry aneurysms)¹. Their prevalence in the general population is around 2%, with a reported prevalence of up to 6.0% in prospective angiographic studies². They are typically located in the areas of arterial bifurcations, with 85% of saccular aneurysms affecting the circle of Willis^{2,3}. Up to 90% of cerebral aneurysms occur in the arteries located in the front part of the brain, the internal carotid artery and its branches⁴. The single most common location, with about 35% of all lowed by the internal carotid artery (30%) and middle cerebral artery (22%)³. Aneurysms of the posterior circulation are most commonly located on the basilar artery tip (5%)⁵. Multiple aneurysms are found in approximately 30% of patients². Depending on the size, aneurysms are divided into very small (≤ 3 mm), small (4-9 mm), large (≥10 mm) and giant (≥25 mm). About 93% of aneurysms in the adult population have a diameter of less than 10 mm². Another important factor for both prognostic and therapeutic purposes is the width of the neck. Aneurysms with a wide neck, defined as neck width ≥4 mm, are less favorable for coiling. However, the dome-to-neck ratio is even more significant. Aneurysms in which this ratio is greater than 2 are considered to be ideal for endovascular treatment⁶. Estimating the impact of aneurysm size on the final outcome is very controversial. Some studies have shown an association of small aneurysms with

aneurysms, is the anterior communicating artery, fol-

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extensive subarachnoid hemorrhage^{7,8}. Still, poor outcome is shown to be more likely in patients with larger aneurysms (10 mm).

It is important to note that most aneurysms remain undetected until they rupture, leading to subarachnoid hemorrhage. Patients typically experience sudden headache (describing it as "worst headache in life"), often accompanied by nausea and vomiting, drowsiness, confusion, and/or loss of consciousness, visual abnormalities and meningism9. According to various studies, up to 17% of patients die immediately¹⁰, and another 25% during hospital care¹¹. Studies show that the final outcome can be predicted by a triad of factors, these being age, clinical condition of the patient on admission measured by Hunt and Hess grade, and presence of vasospasm¹². The highest incidence of rebleeding, about 15%, is during the first 24 hours after rupture¹³. About 20% of aneurysm rebleeding occurs within the first 2 weeks, 30% within the first month, and 50% within 6 months. The mortality of repeated subarachnoid hemorrhage is up to 50%¹⁴. Over time, the risk of rebleeding gradually decreases to a constant of about 3% per year¹⁵. The consequences of aneurysm rupture are severe, and one-third of patients who survive remain dependent on a caregiver, and only up to 20% have no reduction in the quality of life¹⁶.

Given the high morbidity and mortality, it is extremely important to determine the probability of rupture to make an informed decision on whether treatment, which also carries a certain risk, is necessary. Results of the International Study of Unruptured Intracranial Aneurysms (ISUIA), the most significant and largest study of intracranial aneurysms, showed the average annual rate of rupture to be significantly lower than previously estimated¹⁷. This study showed that patients without a history of subarachnoid hemorrhage with aneurysms that were less than 10 mm in diameter had a low annual risk of rupture of approximately 0.05%, whereas patients with a history of subarachnoid hemorrhage with aneurysms of the same size had an approximately 11 times higher risk¹⁷. The annual rate of rupture for large aneurysms was shown to be around 1%. In later revisions, the ISUIA group reduced the critical aneurysm size to 7 mm¹⁸. This is in line with clinical experience that the diameter of ruptured aneurysms is usually lower than 10 mm¹⁹. It is also recognized that aneurysms located on the anterior communicating artery have a significantly higher chance of rupture than other aneurysms of the anterior circulation²⁰.

Diagnostics

The diagnostic method of choice for early detection of subarachnoid hemorrhage and other possible consequences and complications of aneurysm rupture is computerized tomography (CT). CT sensitivity decreases over time due to bleeding, which is no longer observable after 7 days^{21,22}. Subarachnoid hemorrhage can be diagnosed in 95% of cases within the first 2 days. CT determines the amount of blood in the subarachnoid space and ventricular system. CT enables determining ventricular width, associated bleeding, ischemia, blood volume in the cisterns and fissures, also predicting the localization of ruptured aneurysms with a confidence of 78%^{21,22}. CT angiography enables visualization of the cerebral vasculature due to a rapid injection of an iodine contrast agent (3-4 mL/s to a total of 65-70 mL/s). Today, many centers use CT angiography as the only diagnostic method for detecting cerebral aneurysms with a sensitivity of 97%. CT is also important in preoperative planning due to the possibility of a three-dimensional image^{23,24}. Magnetic resonance imaging (MRI) is not a standard method of choice in patients with subarachnoid hemorrhage. In the first 24 to 48 hours of bleeding, MRI sensitivity is not sufficient for subarachnoid hemorrhage diagnosis. The sensitivity of this method increases after 4 to 7 days of bleeding. The fluid-attenuated inversion recovery (FLAIR) MRI recording technique enables better sensitivity²⁵. MR angiography (MRA) can serve as a good screening method for patients at a higher risk, with 87% sensitivity and 92% specificity. Transcranial Doppler (TCD) is a noninvasive method of measuring blood flow through intracranial arteries. As it is a noninvasive method, it is particularly useful in assessing development of vasospasm in patients with subarachnoid hemorrhage. Lumbar puncture was for years the first diagnostic procedure performed in patients with suspected subarachnoid hemorrhage. Cerebrospinal fluid (CSF) obtained by lumbar puncture indicates bleeding in the subarachnoid space. A positive finding is present 2 to 4 hours after bleeding and in 40% of patients remains positive even after 4 weeks. Occasionally, false-positive results are found in traumatic punctures when CSF obtained is contaminated by

	Factors in favor of surgical treatment	Factors in favor of endovascular treatment
Age	Younger age	>75 years
Location	Aneurysm of the middle cerebral artery	Surgically inaccessible aneurysms
Size	Giant aneurysms larger than 20 mm and aneurysms less than 2 mm	Between 2 and 20 mm
Wide neck	Wide aneurysm neck	Aneurysm neck less than 5 mm
Clinical	Unruptured cerebral aneurysms that have a compressive effect on cranial nerves	Severe clinical picture
Procedural	Residual filling after endovascular coiling	Aneurysms for which clipping is not advisable

Table 1. Factors in favor of surgical treatment and endovascular treatment²⁹

blood from epidural blood vessels. Cerebral angiography is crucial for determining the origin of bleeding. Digital subtraction angiography (DSA) has a great advantage in relation to conventional angiography with a positive finding in around 20% of cases of subarachnoid hemorrhage described negatively by angiography²⁶. There is still a possibility of false-negative results in cases where there is a small blood vessel rupture or if the aneurysm is not visible due to temporary occlusion of the neck or the artery (frequency up to 3%). Keeping this in mind, in case of a negative angiography result, it is recommended to repeat cerebral angiography after one month^{27,28}. The best time to perform angiography is in the first 24 hours after rupture, immediately followed by an operative procedure in case of positive finding. If it is not possible to perform angiography in the first 24 hours, it is better to postpone it after the highest risk of vasospasm and rebleeding, which most commonly occur between 4 and 10 days after subarachnoid hemorrhage. Re-ruptured aneurysms significantly reduce the chance of survival.

Treatment of Intracranial Aneurysms

The treatment strategy of unruptured intracranial aneurysms is based on the risk factors for the growth and rupture of aneurysms and availability of therapeutic options for achieving final occlusion (Table 1). The goal of isolating the aneurysm from normal circulation without occluding any small nearby perforating arteries can be achieved with open surgery (craniotomy) by directly clipping the aneurysm neck, or with an endovascular approach by coiling. There are no strict protocols. Conservative, endovascular therapy and microsurgical occlusion should be discussed by the multidisciplinary cerebrovascular team for each patient.

Conservative medical management

Due to improvement of brain imaging methods, the number of incidentally detected aneurysms is increasing, raising the question of whether it is necessary to treat patients who present with an asymptomatic intracranial aneurysm. Decision on the treatment strategy of unruptured intracranial aneurysms is very complex and is based on weighing the risk of rupture and the risk of the intervention itself. However, predicting the risk of rupture is challenging and there are a few methods for estimating the 5-year aneurysm rupture risk. The PHASES score (standing for Population, Hypertension, Age, Size, Earlier subarachnoid hemorrhage, and Site) is based on a set of routinely assessed patient (age, hypertension, history of subarachnoid hemorrhage, and geographical region) and aneurysm (size and location) characteristics³⁰. A higher PHASES score is associated with an increased risk of aneurysmal growth and can, therefore, be used as a marker for aneurysm rupture³¹. By including aneurysm shape, the ELAPSS system (standing for Earlier subarachnoid hemorrhage, Location of the aneurysm, Age, Population, aneurysm Size and Shape) estimates the actual risk of growth more accurately than the PHASES score³². On the other hand, the UIATS (Unruptured Intracranial Aneurysms Treatment Score) relies more on clinical experience than on published data³¹.

A decision on the conservative or interventional management can be supported by the above-mentioned scores, but final decision is based on the assessment of each individual case. In the case of conservative management, regularly scheduled follow up imaging assessments for aneurysm growth or morphological changes should be performed with reduction of the rupture risk factors in terms of blood pressure control and smoking cessation.

Surgical treatment of intracranial aneurysms

Surgical treatment of unruptured intracranial aneurysms means isolating the aneurysm from the normal circulation by clipping of the aneurysm neck. Also, in the case of aneurysm rupture, surgical treatment eliminates the source of bleeding and simultaneously prevents recurrent bleeding. Aneurysm surgery is now greatly facilitated by the introduction of microsurgical procedures, enabling access to almost all intracranial aneurysms. The most important prognostic factor of surgical treatment is whether the aneurysm is intact or it has ruptured. Other factors include aneurysm size and location, as well as patient characteristics (comorbidities, family history, and age)³¹. There are no widely accepted protocols regarding treatment of unruptured intracranial aneurysms and therapeutic decision-making is complex. The factors in favor of surgical treatment include the existence of subarachnoid hemorrhage caused by another aneurysm, symptomatic aneurysms, and aneurysm diameter greater than 5 mm in case of a young or middle-aged patient. On the other hand, surgical results are shown to be significantly less favorable for very large and giant cerebral aneurysms, as well as those located in the posterior circulation^{33,34}.

In case of a ruptured aneurysm, the main goal of surgery is prevention of rebleeding. Most of repeated bleedings occur in the two-week time-window after aneurysm rupture³⁵. Therefore, immediate surgery should be done as soon as possible, preferably within 48 hours of aneurysm rupture. It is known that vasospasm can occur about 4 days after bleeding, often leading to development of ischemia and brain tissue edema, and significantly increasing surgical morbidity and mortality³⁶. Therefore, in the event of delayed surgery, it is important to wait for 10 to 14 days for the aforementioned complications to be resolved and then proceed with the neurosurgery treatment³⁷. Timing of surgery depends on the patient clinical condition, aneurysm localization, and present complications of subarachnoid hemorrhage. The factors affecting the decision on whether an urgent or delayed procedure to perform are the risk of rebleeding, presence of vasospasm, clinical condition of the patient, blood volume in the subarachnoid area verified by CT scan, patient age, existing chronic disease, brain tissue edema verified by CT scan, localization and aneurysm form, presence of intraparenchymal bleeding or other complications, experience of the operating team, and time from

aneurysm rupture to patient reception³⁸. In case of early surgery, the risk of rebleeding and vasospasm is reduced and long-term complications are less likely with shorter hospitalization time. One prospective study showed that the timing of surgery did not significantly affect surgical outcome, promoting early surgery to avoid the known risk of rebleeding and to reduce hospital care³⁸.

Endovascular treatment of intracranial aneurysms

The history of development of endovascular therapy of intracranial aneurysms began in 1964 with the first catheterization of intracranial arteries with microcatheters³⁹, but significant progress was made only in the 1970s by using detachable balloons⁴⁰. The morbidity and mortality rates of this novel technique were very high and it could not be used for the treatment of ruptured aneurysms. The biggest improvement of endovascular treatment occurred in the early 1990s, when Guglielmi et al. published data on endovascular embolization of basilar tip aneurysms with detachable coils^{41,42}. These coils were very soft, each different in shape, with adaptable form, and they could be repositioned several times⁴³. The procedure was less traumatic with shorter recovery time. The first clinical results were excellent and the method was accepted in clinical use^{44,45}. There was a significantly lower percentage of disability or death in patients treated with endovascular procedures compared to data after surgical treatment (23.7% vs. 30.6%). Further monitoring of patients showed that the difference in clinical outcome remained significant after 5 years, especially in terms of the risk of death, while the percentage of patients with disability remained equal^{46,47}. A systematic review showed that the calculated risk of bleeding after endovascular treatment per patient-year was 0.2% (99% CI: 0.1%, 0.3%), but it was limited with short follow up observation periods⁴⁸. The first prospective study on immediate clinical outcome in patients treated with endovascular methods was published in 2008 showing morbidity and mortality rates of 1.7% and 1.4%, respectively. The procedure failed in 4.3% and technical adverse events occurred in 15.4% of patients⁴⁹.

The purpose of coiling is complete and permanent exclusion of aneurysm lumen from the circulation with preservation of the artery. The coils cause blood stasis and thrombosis leading to endothelialization of the aneurysm neck⁵⁰. Complete occlusion is not always

achievable^{51,52}, and a high recurrence rate after coiling is still a major backdrop. A significant benefit of endovascular treatment is that this approach is less invasive compared to open surgery, but it is not suitable for wide-neck aneurysms. Treatment of wide-neck aneurysms is possible with newer methods such as balloon assisted coiling (BAC), stent assisted coiling (SAC), flow diversion (FD), and intrasaccular flow disruption. According to most authors, recurrent aneurysms appear in 20% of embolized patients⁵³⁻⁵⁵. It is believed that the recurrence of aneurysm after coil embolization is due to a progressive growth in the 'unsecured' space within the incompletely filled aneurysm or at the site of the structurally changed wall of the artery. Also, instability of the thrombus-coil complex can lead to acute or delayed luminal recanalization⁵⁶.

Conclusion

Different approaches to intracerebral aneurysm management have different risk-benefit profiles. The most serious complication of both clipping and coiling is rupture, causing massive intracerebral hemorrhage. In case of intraoperative aneurysmal rupture, surgery has the advantage of better hemorrhage control because of direct access to the site of bleeding. Another serious complication is ischemic stroke with consequences depending on aneurysm location and procedure type. The outcome of the procedures depends primarily on the localization and present bleeding of the aneurysm, but also on the patient underlying medical condition. Considering the risks, the choice of treatment for intracranial aneurysms should be made carefully by balancing treatment risk and the risk of rupture. Both methods, surgical clipping and endovascular coiling, are very valuable in treating intracranial aneurysms with benefits and risks, and on choosing the treatment, the physician should approach each patient as a unique case.

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Sažetak

DIJAGNOSTIČKE I TERAPIJSKE NEDOUMICE U LIJEČENJU INTRAKRANIJSKIH ANEURIZMA

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Intrakranijske aneurizme prisutne su u oko 2% populacije. Uobičajen su slučajni nalaz neinvazivnih neuroslikovnih metoda otvarajući pitanje nužnosti liječenja bolesnika s asimptomatskom intrakranijskom aneurizmom. Dugo je jedina mogućnost liječenja bila kirurško podvezivanje vrata aneurizme, no u posljednjih 25 godina usavršen je endovaskularni pristup pružajući alternativu bolesnicima koji ne ispunjavaju uvjete za neurokirurške zahvate. Istraživanja su pokazala bolje rezultate embolizacijskih postupaka s nižim stopama komplikacija, ipak, veća stopa rekanalizacija i dalje je glavni nedostatak endovaskularnog pristupa. Ne postoje strogi protokoli tretiranja intrakranijskih aneurizma te konačna odluka leži u dijalogu između liječnika i bolesnika. Cilj ovoga preglednog rada jest pružiti uvid u pristup intracerebralnim aneurizmama s naglaskom na probleme donošenja odluka s kojima se suočavaju kliničari.

Ključne riječi: Intrakranijske aneurizme; Embolizacija; Podvezivanje; Liječenje