

Pathogenesis and Treatment Strategy of Intracranial Aneurysm

Gang Li *

Chongqing Medical University, Chongqing 400000, China

* Corresponding author Email: lg9812181@163.com

Abstract: Intracranial aneurysm (IA) is a common cerebrovascular disease. Rupture of intracranial aneurysm can lead to subarachnoid hemorrhage, which is characterized by high mortality and poor prognosis. Once onset, the disease develops rapidly, seriously threatening people's life and health. Because intracranial aneurysms start insidiously and don't have corresponding clinical symptoms until they rupture, many patients miss the best opportunity for treatment. Even if you visit the medical center in time, there will be corresponding complications during the treatment. In recent years, with the continuous improvement of molecular biotechnology, the diagnosis and treatment of intracranial aneurysms have made great progress. This article reviews the recent progress in diagnosis, pathogenesis and postoperative treatment of intracranial aneurysms.

Keywords: Intracranial Aneurysm; Pathogenesis; Subarachnoid Hemorrhage; Diagnosis.

1. Introduction

Intracranial aneurysm is a common cerebrovascular disease, which usually has no obvious symptoms when it is not ruptured, but once it is ruptured, it may lead to subarachnoid hemorrhage, leading to serious neurological dysfunction and even death. The mortality rate after the first hemorrhage of an intracranial aneurysm can reach 35%, and the mortality rate after the second hemorrhage increases to 60% to 80%. The causes of intracranial aneurysm rupture are complex and varied, but hypertension, arteriosclerosis and genetic factors are widely considered as the main risk factors for intracranial aneurysm onset and subsequent rupture. Therefore, how to make early diagnosis and treatment of intracranial aneurysm has very important clinical significance. According to the condition of patients with intracranial aneurysms, the risk of surgery is divided into five levels (Hunt-Hess scale), and the patient's condition is assessed by different scales. The grading criteria are as follows: Grade 0: unruptured aneurysms with or without neurological symptoms and signs; Grade I: asymptomatic or mild headache and mild neck stiffness; Grade II: moderate to severe headache, stiff neck, or cranial nerve paralysis; Grade III: drowsiness or confusion with mild focal neurological impairment; Grade IV: Coma, moderate or severe hemiplegia. Level V: Deep coma, decerebration, near-death state; Patients with different grades of intracranial aneurysms need different treatment strategies. In this paper, we summarize the pathogenesis, diagnosis, treatment and other clinical aspects of intracranial aneurysms in order to further understand and study intracranial aneurysms.

2. Pathogenesis of IA

At present, there is no clear conclusion on the pathogenesis of intracranial aneurysm, but a large number of studies have made important breakthroughs in the pathogenesis. Studies have shown that gender (female), advanced age, history of high blood pressure, diabetes, smoking, drinking, and genetic factors are related. At present, the opinions of domestic and foreign experts indicate that the hemodynamic changes

caused by congenital or acquired vascular intima injury may be the main mechanism of intracranial aneurysm [1]. Hypertension, diabetes, and atheromatous plaque formation all destroy the intima of the blood vessel wall to a certain extent, leading to the generation of chronic inflammatory response, and then produce hemodynamic changes. Hypertension may lead to eddy currents in the blood flow of intracranial arteries at the bend of blood vessels. With the fluctuation of blood pressure, the impact on the intima cells of blood vessels is constantly exerted, which also promotes the formation of inflammation in the intima of blood vessels. With the activation and infiltration of inflammatory cells, the intima of blood vessels wall is raised [2]. Relevant studies have concluded that ACE (angiotensin converting enzyme) gene, elastin gene (ELN) and matrixmetalloproteinase gene (MMP) are related to the incidence of intracranial aneurysms [3]. This may provide a new research direction for the diagnosis, treatment and prevention of intracranial aneurysms. ACE gene is located on chromosome 17. According to different gene expression, ACE gene can be divided into three genotypes: insertion homozygote type (II), heterozygote type (ID type) and deletion homozygote type (DD type). Different genotypes may have different expression roles in different race types. Studies have shown that the ACE II genotype is the susceptibility gene of IA in China, while the ACEDD genotype may be its protective genotype, which may have reference significance for targeted gene therapy [4]. ELN gene is mainly responsible for encoding the generation of elastin, which is the main protein for the contraction and expansion of blood vessel wall. Many domestic and foreign studies have shown that the loss of expression of ELN gene is an important factor in the generation of intracranial aneurysm [5]. However, due to regional differences, there is no unified conclusion on the role of ELN gene in the generation of intracranial aneurysm.

3. Diagnosis of IA

Intracranial aneurysm itself does not produce corresponding symptoms and signs for patients, so the diagnosis of intracranial aneurysm mainly relies on predictive

vascular examination. More patients are diagnosed after subarachnoid hemorrhage caused by intracranial aneurysm rupture, resulting in corresponding neurological impairment. Because of its wide availability, rapidity and easiness, CT is the first choice for the initial diagnosis of patients with neurological impairment. In patients with unruptured aneurysms, it is difficult to directly detect aneurysms by conventional CT examination. Once aneurysms rupture and hemorrhage occur, obvious subarachnoid hemorrhage can be seen by CT plain scan. CTA can directly observe the size, number, shape and other important data of intracranial aneurysms through three-dimensional reconstruction of blood vessels on the basis of CT, and is the first choice of imaging examination for patients suspected of having intracranial aneurysms. However, CTA also has its limitations. For example, in the process of image processing of CTA, in order to visually evaluate the surgical indications of aneurysms, it is necessary to process the skull, brain tissue, drainage veins and other interference information around blood vessels through software, so that the diagnosis of small aneurysms (< 2mm) is prone to miss diagnosis. It is also easy to produce false positives for localized vascular enlargement (conus arteriosus) at some branches, which is also the limitation of CTA in diagnosing intracranial aneurysms [5]. DSA (digital subtraction angiography) is the gold standard for the diagnosis of intracranial aneurysms. Through software processing, DSA can directly observe the morphology of intracranial blood vessels without filling of bones and soft tissues during image generation, so it has higher accuracy than CTA [6]. However, DSA angiography is an invasive procedure, which has disadvantages such as greater trauma, higher cost and cumbersome operation compared with CTA. Therefore, in the diagnosis process of intracranial aneurysm, it is necessary to comprehensively consider the patient's condition and use appropriate examination methods.

4. Perioperative Treatment of IA

Since the 1970s, with the continuous upgrading of minimally invasive technology, the development of surgical methods has been promoted, mainly with craniotomy clipping and endovascular spring embolization as the main treatment methods for the reconstruction of tumor bearing arterial hemodynamics, and gradually to the development of complex surgery. Each of the two treatment schemes has its advantages and disadvantages. At present, there is no uniform conclusion on the superiority of the two treatment schemes. However, with the upgrading and development of material technology and the continuous accumulation of aneurysm treatment experience, endovascular therapy has gradually become the mainstream choice for the treatment of intracranial aneurysms. Craniotomy can expose a large range of brain tissue under the microscope, directly observe the aneurysm and the carrying artery, and clamp the aneurysm neck through the aneurysm clip to block the blood supply of the aneurysm, especially for patients with middle cerebral artery aneurysms and ruptured aneurysms combined with intracranial hematoma. With the blockage of aneurysm blood supply, the risk of aneurysm rupture can be significantly avoided, but at the same time, intracranial infection, brain edema and other complications may occur after long-term craniotomy, and the postoperative recovery time of patients is long, and the pain of the postoperative recovery process is also an important factor influencing patients' choice of surgical methods. Endovascular treatment has the advantages of shorter

operation time, less trauma and faster recovery compared with the neoplastic neck closure. In order to treat intracranial aneurysm, intracranial aneurysm stent-assisted intervention has become a common treatment. Stent-assisted interventional embolization technique can isolate the tumor cavity from the carrying artery, prevent the spring ring from herniating into the carrying artery and blocking the blood supply artery. On the other hand, stents can change the hemodynamics in the neck and cavity of the tumor and promote the formation of thrombus around the spring ring in the aneurysm. In the past few decades, great progress has been made in stent-assisted intervention for intracranial aneurysms. However, intravascular therapy can also cause serious complications, including acute cerebral infarction and intravascular thrombosis, and thromboembolism complications occur in 2%-15% of patients with intracranial aneurysms after intravascular therapy. Therefore, both preoperative antiplatelet therapy and intraoperative heparinization are essential in endovascular therapy [7]. Studies have shown that the use of antithrombocytopenesis drugs does not increase the risk of aneurysm rupture during the treatment of unruptured aneurysms. In addition, after endovascular therapy, aggressive antiplatelet therapy was associated with reduced mortality and better functional outcomes in patients with ruptured aneurysms without an increased incidence of postoperative bleeding complications.

Early research results indicated that platelet aggregation function may be decreased in patients with aSAH, which may indirectly lead to postoperative rebleeding in patients with aSAH [8,9]. The mechanism of action may be related to the damage of the blood-brain barrier after subarachnoid hemorrhage, resulting in excessive tissue factors entering the circulation, resulting in the decline of normal platelet function. Some studies have shown that diabetes mellitus, large aneurysm (> 10mm), and aneurysm location (internal carotid arterio-posterior communication artery) are risk factors for postoperative ischemic complications after endovascular therapy for aneurysms [10]. According to relevant studies, the prevention of ischemic complications is more closely related to oral antiplatelet drugs before surgery and intraoperative heparinization [11,12]. Studies have shown that early postoperative antiplatelet therapy is a risk factor for bleeding complications after intravascular therapy for ruptured cerebral aneurysms [13,14], which may be due to the fact that early aneurysm intervention accompanied by early anticoagulation therapy indirectly leads to bleeding complications during the course of the disease. Therefore, delayed antiplatelet therapy can be selected in the treatment regimen to reduce the incidence [15].

In addition to the improvement of surgical techniques, postoperative treatment options have also been further studied and explored. Traditional postoperative treatment options include anticoagulant therapy and antiplatelet therapy to reduce the risk of stent thrombosis and restenosis. However, these treatment options can lead to bleeding and other complications [16,17]. Therefore, in recent years, new postoperative treatment schemes have been proposed, such as anti-coagulation and anti-platelet combined therapy with a variety of drugs. These new treatment options may reduce the occurrence of bleeding and ischemic complications [18,19].

In addition, with the deepening of gene and biomarker research, personalized therapy has also become a research hotspot. By analyzing a patient's genetic background and biomarker levels, doctors can predict the effect of treatment

and develop a more rational postoperative antithrombotic treatment plan. For example, improve the metabolic types of drug genes such as clopidogrel during hospitalization, and adjust the drug usage and dosage according to the examination results. This method of individualized treatment can improve the effect of treatment and reduce the risk of treatment.

In summary, we can see the improvement of materials and instruments, the innovation of postoperative treatment and the development of individualized treatment in the development of stent-assisted interventional treatment for intracranial aneurysms. These advances have made the application of this technology in clinical practice increasingly safe and effective, providing better treatment outcomes for patients. However, there are still some challenges to overcome, such as the risk of thrombosis and complications and the evaluation of long-term effects. Therefore, future studies are needed to further explore these issues in depth and further improve and perfect treatment options.

5. Future Development of IA

At present, with more and more in-depth research on the pathophysiology of aneurysmal subarachnoid hemorrhage, more and more treatment directions are being explored. Good progress has been made in the repair of injured axons, secondary neuronal injury, postoperative complications such as inflammation, brain edema, intracranial ischemia, intracranial hypertension and so on. However, the standard treatment of intracranial aneurysms after interventional surgery is still inconclusive. Currently, there are not enough large, multicenter, prospective clinical studies to generate standardized, systematic treatment options. It is possible that TEG detection and platelet function monitoring in the perioperative period of aneurysm patients can help us adjust the corresponding treatment plan.

References

- [1] Etmnan N, Rinkel GJ. Unruptured intracranial aneurysms: development, rupture and preventive management. *Nat Rev Neurol*. 2016 Dec;12(12):699-713. doi: 10.1038/nrneurol.2016.150. Epub 2016 Nov 3. Erratum in: *Nat Rev Neurol*. 2017 Feb 1;13(2):126. doi: 10.1038/nrneurol.2017.14. PMID: 27808265.
- [2] Khan D, Cornelius JF, Muhammad S. The Role of NF- κ B in Intracranial Aneurysm Pathogenesis: A Systematic Review. *Int J Mol Sci*. 2023;24(18):14218. Published 2023 Sep 18. doi: 10.3390/ijms241814218.
- [3] Zhang X, Ares WJ, Taussky P, Ducruet AF, Grandhi R. Role of matrix metalloproteinases in the pathogenesis of intracranial aneurysms. *Neurosurg Focus*. 2019;47(1):E4. doi:10.3171/2019.4.FOCUS19214.
- [4] Yi Liu, Peng Li, Xiao Hu, Yu Hu, Hao-Gen Sun, Wei-Chao Ma, Fei Qiao, Min He, Chao You. Angiotensin-converting enzyme insertion/deletion gene polymorphism and risk of intracranial aneurysm in a Chinese population[J]. *Journal of International Medical Research*, 2013, 41 (4): 1079-1087.
- [5] Chen Zhixing, Ma Junpeng, Cen Ying, Liu Yi, You Chao. The angiotensin converting enzyme insertion/deletion polymorphism and intracranial aneurysm: a meta-analysis of case-control studies. *Neurol India*. 2013;61(3):293-299. doi:10.4103/0028-3886.115071.
- [6] Chen Xiaodan, Liu Yun, Tong Huazhang, Dong Yonghai, Ma Dongyang, Xu Lei, Yang Cheng. Meta-analysis of computed tomography angiography versus magnetic resonance angiography for intracranial aneurysm.[J]. *Medicine*, 2018, 97 (20): e10771. doi:10.1097/MD.00000000000010771.
- [7] BRACARD S, BARBIER C, DERELLE A L, et al. Endovascular treatment of aneurysms: Pre, intra and post operative management [J]. *European Journal of Radiology*, 2013, 82(10): 1633-1637.
- [8] D'Souza S. Aneurysmal Subarachnoid Hemorrhage. *J Neurosurg Anesthesiol*. 2015;27(3):222-240.
- [9] Lindgren A, Vergouwen MD, van der Schaaf I, et al. Endovascular coiling versus neurosurgical clipping for people with aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2018;8(8):CD003085. doi:10.1002/14651858.CD003085.pub3.
- [10] MATSUKAWA H, KAMIYAMA H, MIYAZAKI T, et al. Analysis for risk factors of 12-month neurological worsening in patients with surgically treated small-to-moderate size unruptured intracranial aneurysms [J]. *Journal of Clinical Neuroscience*, 2018, 58: 160-164.
- [11] HWANG G, JUNG C, PARK S Q, et al. Thromboembolic Complications of Elective Coil Embolization of Unruptured Aneurysms [J]. *Neurosurgery*, 2010, 67(3): 743-748.
- [12] WILSON T J, PANDEY A S, STETLER W R, et al. Dual antiplatelet therapy plus postoperative heparin and dextran is safe and effective for reducing risk of embolic stroke during aneurysm coiling [J]. *Acta Neurochirurgica*, 2014, 156(5): 855-859.
- [13] OHTA T, MURAO K, MIYAKE K, et al. Risk Factors for Early Hemorrhagic Complications after Endovascular Coiling of Ruptured Intracranial Aneurysms [J]. *American Journal of Neuroradiology*, 2014, 35(11): 2136-2139.
- [14] RYU C W, PARK S, SHIN H S, et al. Complications in Stent-Assisted Endovascular Therapy of Ruptured Intracranial Aneurysms and Relevance to Antiplatelet Administration: A Systematic Review [J]. *American Journal of Neuroradiology*, 2015, 36(9): 1682-1688.
- [15] KIM S-T, BAEK J W, LEE W H, et al. Causes of early rebleeding after coil embolization of ruptured cerebral aneurysms [J]. *Clinical Neurology and Neurosurgery*, 2018, 174: 108-116.
- [16] Zhao Long, Lin Ping, Zhang Yi, Huang XingYuan, Li HangYang, Xia MingKai, Huang Xi, Li Zheng, Zhou LiangXue, Tang XiaoPing. Effect of antiplatelet treatment on aneurysmal subarachnoid hemorrhage patients after endovascular treatment: a systematic review with meta-analysis.[J]. *Neurosurgical review*, 2022, 45 (6): 3523-3536.
- [17] NARATA A P, AMELOT A, BIBI R, et al. Dual Antiplatelet Therapy Combining Aspirin and Ticagrelor for Intracranial Stenting Procedures: A Retrospective Single Center Study of 154 Consecutive Patients With Unruptured Aneurysms [J]. *Neurosurgery*, 2019, 84(1): 77-83.
- [18] LUKITO P P, LIE H, HELSA K, et al. Heparin in the treatment of aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis [J]. *Neurosurgical Focus*, 2022, 52(3).
- [19] BRINJIKJI W, MORALES-VALERO S F, MURAD M H, et al. Rescue Treatment of Thromboembolic Complications during Endovascular Treatment of Cerebral Aneurysms: A Meta-Analysis [J]. *American Journal of Neuroradiology*, 2014, 36(1): 121-125.