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Review Article

Basic Knowledge and Overview of Brain AVMs

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Brain arteriovenous malformations (AVMs) are intricate networks of blood vessels in which arteries connect directly to veins, bypassing the capillary system. This aberration can lead to serious neurological manifestations, including seizures, headaches, and hemorrhagic strokes. The embryonic development of AVMs implicates possible disruptions in arteriovenous differentiation during angiogenesis, improper regression of the primary capillary plexus, or the retention of fetal vasculature as contributing factors. Additionally, genetic mutations and environmental influences during pregnancy may facilitate AVM formation, with identified mutations in genes such as endoglin, activin receptor-like kinase 1, SMAD family member 4, and RAS p21 protein activator 1 disrupting vascular development. Such mutations are associated with conditions like hereditary hemorrhagic telangiectasia and capillary malformation-arteriovenous malformation syndrome, thus highlighting the essential role of genetic counseling in AVM management. This review underscores the importance of a deep comprehension of the embryological and genetic foundations of AVMs to refine diagnostic, therapeutic, and prognostic approaches. The paper advocates for advanced research on intervention strategies and emphasizes the significance of a genetics-focused approach in the clinical management of AVMs.

Keywords ▶ brain AVMs, embryology, genetics, endovascular treatment (EVT), angiogenesis

Embryological Aspect of Brain Arteriovenous Malformations (AVMs)

Introduction to brain AVMs

Brain AVMs are complex, web-like tangles of blood vessels where arterial blood flows directly into veins without passing through a normal capillary network. This abnormal vascular structure can lead to a variety of clinical problems, including seizures, headaches, and hemorrhagic strokes. Understanding the embryological development of AVMs is essential for clinicians and researchers in developing prevention and treatment strategies.

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Embryonic development of the vascular system

The vascular system begins to form early in embryogenesis, with blood vessels developing from mesodermally-derived endothelial cells through processes known as vasculogenesis and angiogenesis. Vasculogenesis establishes the initial primitive vascular plexus, while angiogenesis remodels and expands this network. A tightly regulated sequence of genetic and molecular signals is necessary for the normal patterning and differentiation of arteries, veins, and capillaries.[1–3]

Theories on the embryological origin of AVMs

Several theories have been proposed to explain the embryological origins of AVMs. One theory suggests that AVMs result from a disruption in the differentiation between arteries and veins, known as arteriovenous differentiation, which occurs during angiogenesis. Another hypothesis is that AVMs form when the regression of the primary capillary plexus is incomplete or abnormal, preventing the proper formation of the secondary vascular plexus. A third theory posits that AVMs may arise from persistent fetal vasculature that fails to involute postnatally.[4–7]

Disturbances in vascular development leading to AVM formation

Disturbances in the molecular signaling pathways that control vascular development are thought to contribute to AVM formation.[8–10] These include alterations in growth factors, such as vascular endothelial growth factor (VEGF), angiopoietins, and transforming growth factor-beta (TGF-β) and their associated receptors. Genetic mutations affecting these pathways may disrupt the balance between pro-angiogenic and anti-angiogenic signals, leading to the aberrant vessel connections characteristic of AVMs. Additionally, environmental factors during pregnancy, such as hypoxia or exposure to certain substances, may also play a role in the development of AVMs.[4,8,11]

Jeffree et al. recommend delayed angiography for all children with spontaneous intracranial hemorrhage when early angiography is normal, suggesting follow-up between 2 and 5 years after the initial presentation. They argue that the current understanding of AVMs being congenital is not strongly supported by evidence, suggesting that postnatal development may be more common.[5,12]

Genetics of Brain AVMs

Genetic factors associated with AVM development

Brain AVMs are enigmatic vascular lesions whose genesis has long been a subject of investigation. Although the majority of brain AVMs appear sporadically, genetic factors play a crucial role in their development. Mutations in genes responsible for vascular development and integrity, such as endoglin (ENG), activin receptor-like kinase 1 (ACVRL1), and SMAD family member 4 (SMAD4), have been associated with AVMs, especially in hereditary hemorrhagic telangiectasia (HHT). Other genetic alterations include mutations in the RAS p21 protein activator 1 (RASA1) gene, linked with capillary malformation-arteriovenous malformation syndrome (CM-AVM). These genes are involved in the TGF-β signaling pathway, which is critical for blood vessel formation and stability.[8,13–16]

Endothelial-to-mesenchymal transition (EndMT), a specific form of the broader process known as Epithelial-to-mesenchymal transition, is crucial in understanding the pathology of vascular lesions like AVMs.[10,17,18]

During EndMT, endothelial cells, which typically line the interior surface of blood vessels, lose their characteristic markers and gain mesenchymal traits, acquiring the ability to migrate and proliferate. This transformation is significant not only in developmental processes but also in disease pathogenesis, including vascular malformations.[10,17,18]

Several genetic pathways, which are given below, are implicated in the regulation and execution of EndMT. Each contributes to the complex interplay of signaling that governs cellular behavior.

TGF-β pathway

One of the most well-documented pathways in EndMT, TGF-β signaling plays a pivotal role. It promotes the transcription of mesenchymal markers like N-cadherin and vimentin and suppresses endothelial markers such as vascular endothelial (VE)-cadherin. SMAD proteins, particularly SMAD2 and SMAD3, are central to this pathway, transducing signals from the cell surface to the nucleus where they influence gene expression.[8,10,11]

The abbreviation “SMAD” refers to homologies with the Caenorhabditis elegans SMA genes (associated with the “small” worm phenotype) and the MAD family (“mothers against decapentaplegic”) of genes in Drosophila.

Wnt/β-catenin pathway

The Wnt signaling pathway also significantly influences EndMT. Activation of Wnt signaling leads to the stabilization and accumulation of β-catenin in the nucleus, where it acts as a transcription co-activator for genes promoting mesenchymal features. This pathway can synergize with TGF-β signaling to enhance the mesenchymal transition.[8,10,11,19]

Notch signaling

When activated, Notch receptors undergo proteolytic cleavage, releasing the Notch intracellular domain (NICD), which migrates to the nucleus. In the nucleus, NICD works with other transcription factors to induce gene expression that promotes mesenchymal characteristics. Notch signaling has been shown to induce Snail, a transcriptional repressor of E-cadherin, thereby facilitating the mesenchymal transition.[8]

Bone morphogenetic protein (BMP) pathway

Typically associated with bone formation, BMPs also influence vascular development and pathology. Like TGF-β, BMP signaling involves SMAD proteins but can have varying effects on EndMT depending on the context and specific BMP involved.

Hedgehog pathway

Hedgehog signaling contributes to the regulation of EndMT, particularly through its interaction with other pathways like TGF-β. It can modulate the expression of various transcription factors and cytokines involved in the mesenchymal transition process.[10,11]

Phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway

PI3K stands for phosphoinositide 3-kinase, a family of enzymes involved in various cellular functions such as growth, proliferation, differentiation, motility, survival, and intracellular trafficking. The term "Akt" also known as protein kinase B (PKB), is a serine/threonine-specific protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription, and cell migration.

This pathway is crucial for cell survival and proliferation and has been implicated in the EndMT process. Activation of PI3K/Akt signaling can lead to changes in cell adhesion and mobility, characteristic of mesenchymal cells.[8,11,20]

Each of these pathways can be triggered by various stimuli, including mechanical stress, inflammatory cytokines, and changes in the microenvironment, all of which may be relevant in the context of AVM pathology. These pathways are not only involved in EndMT but also play comprehensive roles in the pathogenesis of AVMs. For instance, genetic mutations in these pathways can disrupt the balance between pro-angiogenic and anti-angiogenic signals, leading to abnormal vascular connections characteristic of AVMs. Understanding these pathways not only helps elucidate the molecular mechanisms underlying AVM formation and progression but also may guide the development of targeted therapies to manage or correct these vascular abnormalities.[10,17,18]

Impact on vascular structure

- Loss of Integrity: During EndMT, endothelial cells lose their tight junctions and become more permeable. This loss of endothelial integrity weakens the vessel walls in AVMs.
- Increased Fragility: The transition to mesenchymal cells results in a reduction of structural proteins like elastin and smooth muscle, making the AVM vessels more prone to damage and rupture. The permeability of transformed cells can lead to chronic leakage and microhemorrhages, further destabilizing the AVM and surrounding brain tissue.[10,18]

EndMT plays a significant role in the pathophysiology of unstable AVMs by compromising vascular integrity, increasing the risk of rupture, and exacerbating symptoms. Understanding this process is crucial for developing targeted therapies to stabilize AVMs and prevent complications.[10,18]

Comprehensive role of genetic pathways in AVM pathogenesis

The genetic pathways involved in EndMT, such as TGF-β, Wnt/β-Catenin, and Notch signaling, also have broader implications in the pathogenesis of AVMs.[7,21] Genetic mutations affecting these pathways can lead to the formation and maintenance of abnormal vascular structures:

- ENG, ACVRL1, and SMAD4: Mutations in these genes, which are part of the TGF-β signaling pathway, are associated with HHT, a condition that predisposes individuals to AVMs.[8,22]
- RASA1: Mutations in this gene are linked to CM-AVM, highlighting its role in vascular development and AVM formation.[15,16,23,24]
- VEGF: Dysregulation of VEGF, a key factor in angiogenesis, affects pathways like PI3K/Akt and mitogen-activated protein kinase (MAPK), contributing to abnormal vessel growth seen in AVMs.[7,8,20]

Hereditary conditions known to involve AVMs

AVMs are featured in several hereditary conditions, providing a window into the genetic underpinnings of these vascular anomalies. HHT, also known as Osler-Weber-Rendu syndrome, is the most well-known condition where AVMs are a hallmark feature. Other syndromes include Sturge-Weber syndrome and Wyburn-Mason syndrome. These conditions often have identifiable genetic mutations and exhibit patterns of inheritance that can be autosomal dominant, though penetrance and expression can be variable.[25–30]

Recent genetic studies and discoveries

The advent of next-generation sequencing technologies has accelerated the pace of discovery in the genetics of brain AVMs. Studies have identified somatic mutations in the genes involved in the RAS/MAPK pathway, which are known to contribute to abnormal cell proliferation and vascular endothelial growth. Furthermore, genome-wide association studies (GWAS) have started to reveal polymorphisms that might predispose individuals to sporadic AVMs. Recent research also suggests a potential role for

epigenetic modifications in the pathogenesis of AVMs, although this is an area of ongoing study.[31–34]

Sporadic AVMs and familial AVMs

Sporadic AVMs do not typically follow a hereditary pattern and are believed to arise from somatic mutations—that is, mutations that occur after conception and are not inherited from a parent. These mutations may occur in genes similar to those involved in familial cases (affecting angiogenic and vascular stability pathways) but are not present in the germline. Recent research has identified somatic mutations in the genes involved in the RAS/MAPK pathway, such as Kirsten rat sarcoma viral oncogene homolog (KRAS), neuroblastoma RAS viral oncogene homolog (NRAS), and B-rapidly accelerated fibrosarcoma (BRAF), in tissues from sporadic AVMs. These pathways are crucial in cell proliferation and vascular development. Sporadic AVMs are more common than familial AVMs. They are estimated to occur in approximately 1 in 100000 to 1 in 500000 people per year. The lifetime risk of bleeding from a sporadic AVM is significant, contributing to their medical importance.[4,33,34]

Familial AVMs are thought to occur due to inheritable genetic mutations. These are typically part of genetic syndromes where AVMs are a characteristic feature. For instance, HHT, also known as Osler-Weber-Rendu syndrome, is associated with mutations in the ENG, ACVRL1, and SMAD4 genes. These genes are involved in the signaling pathways that regulate vascular development and stability. Other genetic conditions associated with familial AVMs include CM-AVM caused by mutations in the RASA1 or Ephrin type-B receptor 4 (EPHB4) genes. Familial AVMs are less common than sporadic AVMs. The exact prevalence is difficult to estimate due to the rarity of these conditions and the variability in presentation, but they are a significant concern for individuals with the associated genetic syndromes.[15,16,23]

Somatic mutations in sporadic brain AVMs

Somatic mutations in sporadic brain AVMs are genetic alterations that occur post-zygotically, meaning they are not inherited from a parent but develop in an individual after conception. These mutations are present only in the cells derived from the original mutated cell, which can lead to localized abnormalities such as AVMs in the brain. This contrasts with germline mutations, which occur in the egg or sperm and are passed on to offspring, affecting all cells of the body.

Somatic mutations can arise from various mechanisms, including errors in DNA replication, environmental factors, or failure of DNA repair mechanisms. In the context of brain AVMs, these mutations typically occur in genes that regulate vascular development and stability. Recent research has identified several key genes and pathways implicated in the formation of brain AVMs through somatic mutations. These include genes involved in the RAS/MAPK pathway, such as KRAS, NRAS, and BRAF. These pathways regulate cell growth, differentiation, and survival, and mutations here can lead to uncontrolled vascular endothelial growth and the formation of abnormal vascular connections characteristic of AVMs. Another significant pathway involves the tyrosine kinase with immunoglobulin and epidermal growth factor homology domains 2 (TIE2/TEK) gene, which is crucial for angiogenesis and blood vessel maturation. Somatic mutations in TEK can lead to altered signaling, promoting the development of AVMs.[4,20,23,31,35]

De novo AVMs

De novo formation of brain AVMs refers to the rare occurrence where AVMs develop in patients who previously had no evidence of such vascular anomalies. This phenomenon challenges the traditional belief that AVMs are strictly congenital, suggesting that they can also form postnatally under certain circumstances. The exact mechanisms behind the de novo formation of brain AVMs are not well understood, but several theories and contributing factors have been proposed:

a) Genetic mutations: Some evidence suggests that somatic mutations—those that occur after birth in the cells lining the blood vessels—may contribute to the development of AVMs. For instance, mutations in genes that control vascular growth and stability, such as those involved in the RAS/MAPK and/or notch receptor 2 (NOTCH2) pathway, might initiate the abnormal connections between arteries and veins characteristic of AVMs.[5,36,37]
b) Angiogenic stimuli: External factors that promote angiogenesis (the growth of new blood vessels), such as inflammation, trauma, or hypoxia, may play a role in the formation of AVMs. The body's response to these stimuli involves releasing growth factors like VEGF, which could inadvertently contribute to AVM development if the angiogenic process is dysregulated.
c) Vascular wall abnormalities: Abnormalities in the vascular wall, potentially due to genetic defects or acquired damage, can predispose vessels to form the shunts seen in AVMs. Disruption in normal endothelial cell function can lead to the formation of direct connections between arteries and veins, bypassing the capillary system.

CM-AVM syndrome is identified by numerous small (1–2 cm in diameter) capillary malformations predominantly found on the face and limbs. Additionally, some individuals exhibit AVMs and/or arteriovenous fistulas (AVFs), which are rapid-flow vascular anomalies occurring in the skin, muscles, bones, spine, and brain. These anomalies can lead to serious complications, including bleeding, congestive heart failure, and neurological issues. Symptoms related to intracranial AVMs/AVFs typically emerge early in life. Moreover, a subset of affected individuals present with Parkes Weber syndrome, characterized by multiple micro-AVFs, a distinctive capillary stain on the skin, and pronounced growth of soft tissue and bones in the impacted limb. The diagnosis of CM-AVM syndrome is confirmed in individuals displaying clinical symptoms suggestive of the condition, along with the identification of a heterozygous pathogenic variant in either the EPHB4 or RASA1 genes through molecular genetic testing.[24,38]

Impact on genetic and molecular pathways

Bevacizumab, a monoclonal antibody targeting VEGF, influences the genetic and molecular pathways involved in the angiogenesis and stability of vascular networks in brain AVMs. The effectiveness of bevacizumab can depend significantly on genetic factors that govern VEGF expression and response, highlighting the importance of personalized approaches in the management of brain AVMs. By inhibiting VEGF, bevacizumab directly impacts these angiogenic pathways. The reduction in VEGF activity can lead to decreased endothelial cell proliferation, migration, and survival, reducing the abnormal vascularization seen in AVMs. This inhibition also affects other molecular cascades linked to angiogenesis, including those mediated by endothelial growth factor receptors and other intracellular signaling pathways, such as PI3K/Akt and MAPK, which are involved in cell survival and vascular permeability.[13,39,40] However, it is important to note that bevacizumab is currently not yet approved as the standard treatment option in normal clinical settings. Its use is often considered in specific clinical trials or under particular circumstances where traditional treatment modalities have not been effective or are not suitable.

The role of genetic testing and counseling in AVMs

Genetic testing can identify mutations associated with hereditary conditions predisposing individuals to AVMs, thereby aiding in the diagnosis, management, and familial risk assessment. Prenatal testing and preimplantation genetic diagnosis may be considerations for families with known hereditary conditions. Genetic counseling is vital in interpreting test results, understanding the risks of recurrence in families, and discussing the implications of genetic findings. Counseling can guide surveillance strategies for at-risk individuals and inform decisions regarding family planning and management of the condition.[20,37,41]

Types of Brain AVMs and Unclassified Arteriovenous Shunts (AV-shunts)

Classification of brain AVMs

Brain AVMs are traditionally classified based on three primary characteristics: size, location within the brain, and venous drainage patterns. The Spetzler-Martin grading system is widely used to categorize AVMs and guide treatment decisions. This system scores AVMs based on their size (small, medium, large), the eloquence of the adjacent brain tissue (non-eloquent or eloquent), and the pattern of venous drainage (superficial or deep). The higher the score, the more complex the AVM and the higher the surgical risk. However, the Spetzler-Martin grading system may not provide detailed information on these aspects, which are critical for planning and executing endovascular procedures. Additionally, the Spetzler-Martin grading system does not directly correlate with the likelihood of achieving complete obliteration of the AVM through endovascular means or with the risk of complications from embolization. Therefore, while it is a valuable tool for surgical planning, it may not be as useful for planning endovascular treatments, which require a different set of criteria for risk assessment and procedural strategy.[42–44]

Description of each type and their clinical significance

- Small AVMs are less than 3 cm in diameter and are often considered for surgical resection due to a relatively lower risk of complications.
- Medium AVMs range from 3 to 6 cm and may require multimodal treatment approaches.
- Large AVMs are over 6 cm and present significant treatment challenges due to increased surgical risks; they are often managed conservatively or treated with staged procedures.
- In terms of location, AVMs can be found in “non-eloquent” areas, where treatment is less likely to result in neurological deficits, or “eloquent” regions, which are areas of the

brain responsible for essential functions such as language, sensory processing, or motor function. Treatment in eloquent areas requires more careful consideration due to the higher risk of postoperative deficits.

- Venous drainage is another critical factor; AVMs with exclusively superficial drainage tend to have a more straightforward surgical approach, whereas those with deep venous drainage can be more complex and risky to treat.

Discussion on unclassified AV-shunts

Unclassified AV-shunts are those that do not fit neatly into the established categories of AVMs. They may exhibit unusual feeding artery and draining vein configurations, have a diffuse rather than focal nidus, or may present with atypical clinical symptoms. These unique characteristics often preclude the use of standard classification systems and can complicate diagnosis and treatment.

AVM-look alike-lesions

The term "AVM-look alike-lesions" (false cerebral AVMs) refers to various vascular abnormalities in the brain that mimic the appearance of AVMs in imaging studies but differ in their pathology, clinical significance, and treatment approaches. The explanation of each type is given in the below sections.

Cerebral proliferative angiopathy (CPA)

This refers to conditions characterized by abnormal proliferation of blood vessels that may resemble AVMs: Diffuse AVM is an extensive vascular malformation that covers a large area of the brain. Giant AVM refers to a particularly large AVM, which significantly increases the risk of hemorrhage. Angiomatosis involves multiple small blood vessels proliferating in a region, sometimes associated with genetic conditions.

a) Non-hemorrhagic: These are cases where the abnormal vessels have not ruptured, presenting no bleeding.
b) Hemorrhagic: In these cases, the vessels have ruptured, leading to bleeding, which can be a serious and life-threatening condition.

Venous post-thrombotic pial/dural AV-shunt

These are abnormal connections between arteries and veins that develop after a venous thrombosis (a blood clot in a vein). The clotting event can lead to increased pressure and cause the formation of new, abnormal pathways for blood flow as a compensatory mechanism.

Developmental venous anomaly (DVA) with capillary staining

DVAs are common vascular anomalies that are typically benign. However, when accompanied by capillary staining, it indicates increased blood flow in the capillaries associated with the DVA, making it resemble an AVM in imaging studies.

Luxury perfusion (transient)

This is a phenomenon where there is an increase in blood flow to a region of the brain that exceeds the metabolic demand of the tissue. It's usually seen after ischemic stroke or other events where blood flow has been restored to previously deprived brain tissue. It can mimic an AVM due to the high flow appearance on imaging studies but is typically temporary.

Intratumoral AV-shunt

These are AV-shunts found within tumors and can be mistaken for AVMs. They can occur in various types of brain tumors:

a) Glioblastoma: Highly malignant brain tumors that may develop these shunts due to rapid and abnormal vascular growth.
b) Hemangioblastoma: These are benign tumors, often associated with von Hippel-Lindau disease, characterized by high vascularity that can include AV-shunts.
c) Metastasis: Secondary brain tumors from cancers elsewhere in the body might also show abnormal vascular patterns, including AV-shunts.

Each of these conditions presents unique challenges in diagnosis and management, often requiring specialized imaging techniques to differentiate from true cerebral AVMs and tailored therapeutic approaches depending on the underlying pathology and associated risks.

One of the representatives of the unclassified AV-shunts is the CPA. CPA and brain AVM are both vascular disorders of the central nervous system, but they have distinct characteristics, pathophysiology, and clinical implications. Understanding the differences between these two entities is crucial for proper diagnosis, management, and treatment. Here's an overview and comparison of the two conditions:

- Localization: AVMs have a localized nidus, while CPA involves a diffuse area of the brain.
- Vascular architecture: AVMs present a direct arteriovenous shunting through a nidus, whereas CPA involves a

proliferative, diffuse network of vessels without a clear arteriovenous shunting.
- Hemorrhage risk: While both conditions carry a risk of bleeding, the risk is generally considered higher in AVMs due to the high-flow, high-pressure shunting.
- Treatment approach: AVMs can often be treated with targeted interventions aimed at the nidus, whereas CPA's diffuse nature makes surgical intervention more complex and less feasible. Generally, CPA's lesions should not be the target of embolization, irradiation, or surgical resection.

Understanding these differences is crucial for clinicians in diagnosing, managing, and advising patients with these complex cerebrovascular conditions.

Systemic Review of Endovascular Treatment (EVT) with a focus on Transarterial Embolization (TAE)

What EVT encompasses in the context of brain AVMs?

EVT refers to a range of minimally invasive procedures performed within the blood vessels. In the context of brain AVMs, EVT aims to reduce the risk of hemorrhage by occluding the abnormal vascular channels that define the AVM. Techniques employed in EVT include TAE, Transvenous embolization (TVE), and, more recently, Flow-Directed Microcatheter techniques. TAE, the focus of this review, involves the delivery of embolic agents through the arterial network to the AVM nidus, the network of abnormal vessels.[45–51)]

Historical perspective on the treatment of AVMs

The treatment of brain AVMs has evolved significantly since the inception of neurological surgery. Early attempts at intervention were surgical, with varied success and significant risk. The development of angiography revolutionized the understanding and diagnostic approach to AVMs, paving the way for EVT. EVT began with the use of particle embolization in the 1970s and has since progressed to include advanced liquid embolic agents. TAE has become a pivotal tool in the pre-surgical reduction of AVM size and, in some cases, serves as a definitive treatment.[45–47)]

Specific methodologies of EVT, emphasizing TAE

TAE involves the catheterization of feeding arteries and the injection of embolic agents to induce thrombosis within the AVM. The choice of embolic materials is critical and includes polyvinyl alcohol particles, n-butyl cyanoacrylate glue, and Onyx, a non-adhesive liquid embolic agent. Real-time navigation through digital subtraction angiography allows for precise delivery of the embolic material. Advances in microcatheter design and embolic materials have improved the safety and efficacy of TAE, making it a less invasive alternative or adjunct to surgical resection.[52)]

Comparative studies and outcomes of TAE

Comparative studies have evaluated the outcomes of TAE in the management of brain AVMs, often juxtaposing it against surgical resection and stereotactic radiosurgery. The success of TAE is measured by the degree of nidus obliteration, reduction in hemorrhage risk, and patient outcomes, including neurological function and quality of life. While complete obliteration is less commonly achieved with TAE alone compared to surgical resection, TAE can significantly reduce AVM size and hemorrhage risk. Studies have demonstrated that preoperative TAE can facilitate surgical resection by reducing intraoperative bleeding. TAE as a stand-alone treatment is particularly useful in patients with high-surgical-risk AVMs or those in eloquent brain regions. Complications can include ischemic stroke, hemorrhage, and neurological deficits, although the rates have decreased with technical advancements.[53–57)]

TVE

The process and technique of TVE

TVE is an advanced endovascular procedure tailored for the treatment of brain AVMs. This minimally invasive approach involves navigating a catheter through the venous system to reach the abnormal vascular network of the AVM directly. Once the catheter is in place, embolic agents, such as liquid embolics like Onyx, are deployed to occlude the AVM from the venous side. The goal is to disrupt the abnormal blood flow and induce thrombosis within the nidus, which can lead to a reduction in size or complete obliteration of the AVM over time.[48,58,59)]

Indications and contraindications for transvenous embolization

The primary indication for TVE is the presence of an AVM that poses a significant risk of hemorrhage or neurological deficit and is not amenable to traditional surgery or poses a substantial risk if approached transarterially. TVE is

particularly indicated in AVMs with previous hemorrhage, compact nidus, and accessible draining veins. Contraindications include inaccessible AVM location, small feeding veins that prevent safe catheter navigation, and extensive nidus with multiple feeding arteries that would leave residual AVM post-embolization.[48,60,61]

Risks and benefits of the procedure

TVE offers the benefit of a less invasive alternative to open surgery, with a lower risk of immediate hemorrhage during treatment and the potential for complete obliteration of the AVM. It can be particularly beneficial for deep or surgically inaccessible lesions. However, risks remain, including venous perforation, non-target embolization leading to ischemic complications, post-procedure swelling, and potential for hemorrhage if the AVM is not completely obliterated. Postoperative care and monitoring are crucial to manage and mitigate these risks.[49,57,61–63]

Case studies and success rates

Case studies of TVE show varying success rates, often dependent on the size and location of the AVM as well as the patient's overall health. Complete obliteration rates reported in the literature vary, with some studies reporting success in the majority of cases when TVE is used either as a standalone therapy or in conjunction with other modalities like surgery or radiosurgery. Long-term success also depends on follow-up care, with some AVMs requiring multiple embolization sessions. Recanalization, where the AVM reestablishes blood flow after initial treatment, remains a concern, and long-term imaging follow-up is essential.[63,64]

Conclusion

In this comprehensive review, the intricate challenges of diagnosing and managing brain AVMs are highlighted, underlining the critical need to grasp their embryological and genetic bases. AVMs may originate from embryological disruptions in vascular development, such as arteriovenous differentiation or flawed regression of the primary capillary network. Genetic aberrations, particularly in the TGF-β signaling pathway, are pivotal in the emergence of AVMs, with disorders like HHT and CM-AVM being genetically linked. The article calls for further research and improvements in intervention techniques, advocating for tailored treatments and the significance of genetic counseling to enhance outcomes for patients with these intricate cerebrovascular anomalies.

Disclosure Statement

The author has no conflicts of interest.

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