

The background features a repeating pattern of stylized neurons in a light orange color against a darker orange background. A horizontal bar is positioned near the top, consisting of a short grey segment on the left and a longer white segment on the right.

Arteriovenous Malformations

and Other Vascular Lesions
of the Central Nervous System

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
National Institutes of Health

Arteriovenous Malformations and Other Vascular Lesions of the Central Nervous System

Arteriovenous malformations (AVMs) are abnormal, snarled tangles of blood vessels that cause multiple irregular connections between the arteries and veins. These malformations most often occur in the spinal cord and in any part of the brain or on its surface, but can develop elsewhere in the body.

Normally, arteries carry oxygen-rich blood away from the heart to the body's cells, organs, and tissues; veins return blood with less oxygen to the lungs and heart. But in an AVM, the absence of capillaries—a network of small blood vessels that connect arteries to veins and deliver oxygen to cells—creates a shortcut for blood to pass directly from arteries to veins and bypass tissue, which can lead to tissue damage and the death of nerve cells and other cells. Over time, some AVMs get progressively larger as the amount of blood flow increases.

In some cases, a weakened blood vessel may burst, spilling blood into the brain (hemorrhage) that can cause stroke and brain damage. Other neurological problems include headache, weakness, seizures, pain, and problems with speech, vision, or movement. In most cases, people with neurological AVMs experience few, if any, significant symptoms.

It is unclear why AVMs form. Most often AVMs are congenital, but they can appear sporadically. In some cases the AVM may be inherited, but it is more likely that other inherited conditions increase the risk of having an AVM. The malformations tend to be discovered only incidentally, usually during treatment for an unrelated disorder or at autopsy. It is estimated that brain AVMs occur in less than one percent of the general population; each year about one percent of those with AVMs will die as a direct result of the AVM.

Treatment options depend on the type of AVM, its location, noticeable symptoms, and the general health condition of the individual.

What are the symptoms?

Symptoms can vary greatly in severity; in some people the severity of symptoms becomes debilitating or even life-threatening.

Seizures and headaches that may be severe are the most generalized symptoms of AVMs, but no particular type of seizure or headache pattern has been identified. Seizures can be focal (meaning they involve a small part of the brain) or generalized (widespread), involving convulsions, a loss of control over movement, or a change in a person's level of consciousness. Headaches can vary greatly in frequency, duration, and intensity, sometimes becoming as severe as migraines. Pain may be on either one side of the head or on both sides. Sometimes a headache consistently affecting one side of the head may be closely linked to the site of an AVM. Most often, the location of the pain

is not specific to the malformation and may encompass most of the head.

AVMs also can cause a wide range of more specific neurological symptoms that vary from person to person, depending primarily upon the location of the AVM. Such symptoms may include:

- muscle weakness or paralysis in one part of the body
- a loss of coordination (*ataxia*) that can lead to such problems as gait disturbances
- difficulties carrying out tasks that require planning (*apraxia*)
- back pain or weakness in the lower extremities caused by a spinal AVM
- dizziness
- visual problems such as a loss of part of the visual field, inability to control eye movement, or swelling of a part of the optic nerve
- difficulty speaking or understanding language (*aphasia*)
- abnormal sensations such as numbness, tingling, or spontaneous pain
- memory deficits
- confusion, hallucinations, or dementia.

AVMs may also cause subtle learning or behavioral disorders in some people during their childhood or adolescence, long before more obvious symptoms become evident.

Symptoms caused by AVMs can appear at any age. Because the abnormalities tend to result from a slow buildup of neurological damage over

time, they are most often noticed when people are in their twenties or older. If AVMs do not become symptomatic by the time people reach their late forties or early fifties, they tend to remain stable and are less likely to produce symptoms. Some pregnant women may experience a sudden onset or worsening of symptoms due to accompanying cardiovascular changes, especially increases in blood volume and blood pressure.

Although most neurological AVMs have very few, if any, significant symptoms, one particularly severe type of AVM causes symptoms to appear at, or very soon after, birth. Called a *vein of Galen defect* after the major blood vessel involved, this lesion is located deep inside the brain. It is frequently associated with *hydrocephalus* (an accumulation of fluid within certain spaces in the brain, often with visible enlargement of the head), swollen veins visible on the scalp, seizures, failure to thrive, and congestive heart failure. Children born with this condition who survive past infancy often remain developmentally impaired.

How do AVMs damage the brain and spinal cord?

AVMs damage the brain or spinal cord through three basic mechanisms: by reducing the amount of oxygen reaching neurological tissues; by causing bleeding (hemorrhage) into surrounding tissues; and by compressing or displacing parts of the brain or spinal cord.

- AVMs affect oxygen delivery to the brain or spinal cord by altering normal patterns of blood flow using the arteries, veins, and

capillaries. In AVMs arteries pump blood directly into veins through a passageway called a *fistula*. Since the network of capillaries is bypassed, the rate of blood flow is uncontrolled and too rapid to allow oxygen to be dispersed to surrounding tissues. As a result, the cells that make up these tissues become oxygen-depleted and begin to deteriorate, sometimes dying off completely.

- This abnormally rapid rate of blood flow frequently causes blood pressure inside the vessels located in the central portion of an AVM directly adjacent to the fistula—an area doctors refer to as the *nidus*—to rise to dangerously high levels. The arteries feeding blood into the AVM often become swollen and distorted; the veins that drain blood away from it often become abnormally constricted (a condition called *stenosis*). Also, the walls of the involved arteries and veins are often abnormally thin and weak. *Aneurysms*—balloon-like bulges in blood vessel walls that are susceptible to rupture—may develop in association with approximately half of all neurological AVMs due to this structural weakness.
- Bleeding into the brain, called intracranial hemorrhage, can result from the combination of high internal pressure and vessel wall weakness. Such hemorrhages are often microscopic in size (called microbleeds), causing limited damage and few significant symptoms. (Generally, microbleeds do not have short-term consequences on brain function, but microbleeds over time can lead to an increased risk of dementia and cognitive

disruption.) Even many nonsymptomatic AVMs show evidence of past bleeding. But massive hemorrhages can occur if the physical stresses caused by extremely high blood pressure, rapid blood flow rates, and vessel wall weakness are great enough. If a large enough volume of blood escapes from a ruptured AVM into the surrounding brain, the result can be a catastrophic stroke. AVMs account for approximately two percent of all hemorrhagic strokes that occur each year.

- Even in the absence of bleeding or significant oxygen depletion, large AVMs can damage the brain or spinal cord simply by their presence. They can range in size from a fraction of an inch to more than 2.5 inches in diameter, depending on the number and size of the blood vessels making up the lesion. The larger the lesion, the greater the amount of pressure it exerts on surrounding brain or spinal cord structures. The largest lesions may compress several inches of the spinal cord or distort the shape of an entire hemisphere of the brain. Such massive AVMs can constrict the flow of cerebrospinal fluid—a clear liquid that normally nourishes and protects the brain and spinal cord—by distorting or closing the passageways and open chambers (*ventricles*) inside the brain that allow this fluid to circulate freely. As cerebrospinal fluid accumulates, hydrocephalus results. This fluid buildup further increases the amount of pressure on fragile neurological structures, adding to the damage caused by the AVM itself.

Where do neurological AVMs tend to form?

AVMs can form virtually anywhere in the brain or spinal cord—wherever arteries and veins exist. Some are formed from blood vessels located in the *dura mater* or in the *pia mater*, the outermost and innermost, respectively, of the three membranes surrounding the brain and spinal cord. (The third membrane, called the *arachnoid*, lacks blood vessels.) AVMs of the *dura mater* affect the function of the spinal cord by transmitting excess pressure to the venous system of the spinal cord. AVMs of the spinal cord affect the function of the spinal cord by hemorrhage, by reducing blood flow to the spinal cord, or by causing excess venous pressure. Spinal AVMs frequently cause attacks of sudden, severe back pain, often concentrated at the roots of nerve fibers where they exit the vertebrae, with pain that is similar to that caused by a slipped disk. These lesions also can cause sensory disturbances, muscle weakness, or paralysis in the parts of the body served by the spinal cord or the damaged nerve fibers. A spinal cord AVM can lead to degeneration of the nerve fibers within the spinal cord below the level of the lesion, causing widespread paralysis in parts of the body controlled by those nerve fibers.

AVMs on the surface of the *cerebral hemispheres*—the uppermost portions of the brain—exert pressure on the *cerebral cortex*, the brain’s “gray matter.” Depending on their location, these AVMs may damage portions of the cerebral cortex involved with thinking, speaking, understanding language, hearing, taste, touch, or initiating and controlling voluntary movements. AVMs located on the

frontal lobe close to the optic nerve or on the occipital lobe (the rear portion of the cerebrum where images are processed) may cause a variety of visual disturbances.

AVMs also can form from blood vessels located deep inside the interior of the *cerebrum* (the main portion of the brain). These AVMs may compromise the functions of three vital structures: the *thalamus*, which transmits nerve signals between the spinal cord and upper regions of the brain; the *basal ganglia* surrounding the thalamus, which coordinate complex movements and plays a role in learning and memory; and the *hippocampus*, which plays a major role in memory.

AVMs can affect other parts of the brain besides the cerebrum. The *hindbrain* is formed from two major structures: the *cerebellum*, which is nestled under the rear portion of the cerebrum, and the *brain stem*, which serves as the bridge linking the upper portions of the brain with the spinal cord. These structures control finely coordinated movements, maintain balance, and regulate some functions of internal organs, including those of the heart and lungs. AVM damage to these parts of the hindbrain can result in dizziness, giddiness, vomiting, a loss of the ability to coordinate complex movements such as walking, or uncontrollable muscle tremors.

What are the health consequences of AVMs?

The greatest potential danger posed by AVMs is hemorrhage. Most episodes of bleeding remain undetected at the time they occur because they are not severe enough to cause significant neurological damage. But

massive, even fatal, bleeding episodes do occur. Whenever an AVM is detected, the individual should be carefully and consistently monitored for any signs of instability that may indicate an increased risk of hemorrhage.

A few physical characteristics appear to indicate a greater-than-usual likelihood of clinically significant hemorrhage:

- Smaller AVMs have a greater likelihood of bleeding than do larger ones.
- Impaired drainage by unusually narrow or deeply situated veins increases the chances of hemorrhage.
- Pregnancy appears to increase the likelihood of clinically significant hemorrhage, mainly because of increases in blood pressure and blood volume.
- AVMs that have hemorrhaged once are about nine times more likely to bleed again during the first year after the initial hemorrhage than are lesions that have never bled.

The damaging effects of a hemorrhage are related to lesion location. Bleeding from AVMs located deep inside the interior tissues, or *parenchyma*, of the brain typically causes more severe neurological damage than does hemorrhage by lesions that have formed in the dural or pial membranes or on the surface of the brain or spinal cord. (Deeply located bleeding is usually referred to as an *intracerebral* or *parenchymal* hemorrhage; bleeding within the membranes or on the surface of the brain is known as *subdural* or *subarachnoid* hemorrhage.) Therefore, location is an important factor to consider when weighing the relative risks surgery to treat AVMs.

What other types of vascular lesions affect the central nervous system?

Besides AVMs, three other main types of vascular lesion can arise in the brain or spinal cord: *cavernous malformations*, *capillary telangiectases*, and *venous malformations*. These lesions may form virtually anywhere within the central nervous system, but unlike AVMs, they are not caused by high-velocity blood flow from arteries into veins. Instead of a combination of arteries and veins, these low-flowing lesions involve only one type of blood vessel. These lesions are less unstable than AVMs and do not pose the same relatively high risk of significant hemorrhage. In general, low-flow lesions tend to cause fewer troubling neurological symptoms and require less aggressive treatment than do AVMs.

- Cavernous malformations are formed from groups of tightly packed, abnormally thin-walled, small blood vessels that displace normal neurological tissue in the brain or spinal cord. The vessels are filled with slow-moving or stagnant blood that is usually clotted or in a state of decomposition. Like AVMs, cavernous malformations can range in size from a few fractions of an inch to several inches in diameter, depending on the number of blood vessels involved. Some people develop multiple lesions. Although cavernous malformations usually do not hemorrhage as severely as AVMs do, they sometimes leak blood into surrounding tissues because the walls of the involved blood vessels are extremely fragile. Although they are often not as symptomatic as AVMs, cavernous malformations can cause seizures

in some people. After AVMs, cavernous malformations are the type of vascular lesion most likely to require treatment.

- Capillary telangiectases are groups of abnormally swollen capillaries and usually measure less than an inch in diameter. Telangiectases are usually benign and rarely cause extensive damage to surrounding brain or spinal cord tissues. Any isolated hemorrhages that occur are microscopic in size. However, in some inherited disorders in which people develop large numbers of these lesions, telangiectases can contribute to the development headaches or seizures.
- Venous malformations consist of abnormally enlarged veins. The structural defect usually does not interfere with the function of the blood vessels, and venous malformations rarely hemorrhage. As with telangiectases, most venous malformations do not produce symptoms, remain undetected, and follow a benign course.

What causes vascular lesions?

The cause of vascular anomalies of the central nervous system is not yet well understood. Scientists believe the anomalies most often result from mistakes that occur during embryonic or fetal development. These mistakes may be linked to genetic mutations in some cases. A few types of vascular malformations are known to be hereditary and thus are known to have a genetic basis. Some evidence also suggests that at least some of these lesions are acquired later in life as a result of injury to the central nervous system.

During fetal development, new blood vessels continuously form and then disappear as the human body changes and grows. These changes in the body's vascular map continue after birth and are controlled by *angiogenic factors*, chemicals produced by the body that stimulate new blood vessel formation and growth. Researchers have identified changes in the chemical structures of various angiogenic factors in some people who have AVMs or other vascular abnormalities of the central nervous system. However, it is not yet clear how these chemical changes actually cause changes in blood vessel structure.

By studying patterns of occurrence in families, researchers have established that one type of cavernous malformation involving multiple lesion formation is caused by a genetic mutation in chromosome 7. This genetic mutation appears in many ethnic groups, but it is especially frequent in a large population of Hispanic Americans living in the Southwest; these individuals share a common ancestor in whom the genetic change occurred. Some other types of vascular defects of the central nervous system are part of larger medical syndromes known to be hereditary. They include *hereditary hemorrhagic telangiectasia*, *Sturge-Weber syndrome*, and *Klippel-Trenaunay syndrome*.

How are AVMs and other vascular lesions detected?

One of the more distinctive signs clinicians use to diagnose an AVM is an auditory phenomenon called a *bruit*—a rhythmic, whooshing sound caused by excessively rapid

blood flow through the arteries and veins of an AVM. The sound is similar to that made by a torrent of water rushing through a narrow pipe. A bruit can sometimes become a symptom when it is especially severe. When audible to individuals, the bruit may compromise hearing, disturb sleep, or cause significant psychological distress.

An array of imaging technologies can be used to uncover the presence of AVMs. *Cerebral angiography*, also called cerebral arteriography, provides the most accurate pictures of blood vessel structure in brain AVMs. A special water-soluble dye, called a contrast agent, is injected into an artery and highlights the structure of blood vessels so that it can be seen on X-rays. CT scans (*computed axial tomography*) use X-rays to create an image of the head, brain, or spinal cord and are especially useful in revealing the presence of hemorrhage. MRI (*magnetic resonance imaging*) uses magnetic fields and radio waves to create detailed images that can show subtle changes in neurological tissues. *Magnetic resonance angiography* (MRA) can record the pattern and velocity of blood flow through vascular lesions as well as the flow of cerebrospinal fluid throughout the brain and spinal cord. *Transcranial Doppler ultrasound* can diagnose medium-size to large AVMS and also detect the presence and extent of hemorrhage. It evaluates blood flow through the brain by directing high-frequency sound waves through the skull at particular arteries. The resulting sound wave signals that bounce back from blood cells are interpreted by a computer to make an image of the velocity of blood flow.

How are AVMs and other vascular lesions treated?

There are several options for treating AVMs. Although medication can often lessen general symptoms such as headache, back pain, and seizures caused by AVMs and other vascular lesions, the definitive treatment for AVMs is either surgery or focused radiation therapy. Venous malformations and capillary telangiectases rarely require surgery. Cavernous malformations are usually well defined enough for surgical removal, but surgery on these lesions is less common than for AVMs because they do not pose the same risk of hemorrhage.

Because so many variables are involved in treating AVMs, doctors must assess the danger posed to individuals largely on a case-by-case basis. A hemorrhage from an untreated AVM can cause serious neurological deficits or death, leading many clinicians to recommend surgical intervention whenever the physical characteristics of an AVM appear to indicate a greater-than-usual likelihood of significant bleeding and subsequent neurological damage. However, surgery on any part of the central nervous system carries some risk of serious complications or death. There is no easy formula that can allow physicians and individuals to reach a decision on the best course of therapy.

An AVM grading system developed in the mid-1980s can help health care professionals estimate the risk of surgery based on the size of the AVM, location in the brain and surrounding tissue involvement, and any leakage.

Three surgical options are used to treat AVMs: *conventional surgery*, *endovascular embolization*,

and *radiosurgery*. The choice of treatment depends largely on the size and location of an AVM. Endovascular embolization and radiosurgery are less invasive than conventional surgery and offer safer treatment options for some AVMs located deep inside the brain.

- Conventional surgery involves entering the brain or spinal cord and removing the central portion of the AVM, including the fistula, while causing as little damage as possible to surrounding neurological structures. This surgery is most appropriate when an AVM is located in a superficial portion of the brain or spinal cord and is relatively small in size. AVMs located deep inside the brain generally cannot be approached through conventional surgical techniques because there is too great a possibility that functionally important brain tissue will be damaged or destroyed.
- In endovascular embolization the surgeon guides a catheter through the arterial network until the tip reaches the site of the AVM. The surgeon then injects a substance (such as fast-drying glue-like substances, fibered titanium coils, and tiny balloons) that will travel through blood vessels and create an artificial blood clot in the center of an AVM. Since embolization usually does not permanently obliterate the AVM, it is usually used as an adjunct to surgery or to radiosurgery to reduce the blood flow through the AVM and make the surgery safer.
- Radiosurgery is an even less invasive therapeutic approach often used to treat small AVMs that haven't ruptured. A beam of highly focused radiation is aimed directly on the AVM

and damages the walls of the blood vessels making up the lesion. Over the course of the next several months, the irradiated vessels gradually degenerate and eventually close, leading to the resolution of the AVM.

Embolization frequently proves incomplete or temporary, although new embolization materials have led to improved results. Radiosurgery often has incomplete results as well, particularly when an AVM is large, and it poses the additional risk of radiation damage to surrounding normal tissues. Even when successful, complete closure of an AVM takes place over the course of many months following radiosurgery. During that period, the risk of hemorrhage is still present. However, both techniques can treat deeply situated AVMs that had previously been inaccessible. And in many individuals, staged embolization followed by conventional surgical removal or by radiosurgery is now performed, resulting in further reductions in death and complication rates.

What research is being done?

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to seek fundamental knowledge about the brain and spinal cord and to use that knowledge to reduce the burden of neurological disease. NINDS is a component of the National Institutes of Health, the leading supporter of biomedical research in the world. NINDS conducts research on neurological disorders, including AVMs and other vascular lesions of the central nervous system, and supports research through grants to major medical and research institutions across the country.

In partnership with the medical school of Columbia University, NINDS has established a long-term Arteriovenous Study Group to learn more about the natural course of AVMs in people and to improve the surgical treatment of these lesions. A NINDS study at Columbia University, A Randomized Trial of Unruptured Brain AVMs (ARUBA), showed that medical management alone is superior to medical management and interventional therapy (conventional surgery, endovascular procedures, and radiosurgery) for improving the long-term outcome of individuals with unruptured brain arteriovenous malformations. Data from a recently closed observational phase will show if the disparities continued over the additional five years of follow-up.

Hereditary hemorrhagic telangiectasias (HHT) of the brain are difficult to study. A NIH Rare Diseases Clinical Research Consortium (a collection of centers that study different rare diseases and share information) is studying risk factors for bleeding inside the brain in individuals who have an HHT. Data received through the Consortium will help to construct a database, blood sampling and banking (through the NINDS), and genetic analysis that may lead to improved care for individuals with HHT.

Anti-angiogenic therapy uses drugs that either activate and promote cell growth or directly block the growing blood vessel cells. NINDS-funded researchers are testing the anti-angiogenic drug Apo-Timop, part of a class of drugs called beta-blockers, to see if it shrinks HHT, which may lead to the development of new anti-angiogenics for people with vascular malformations.

Non-human models of disease are invaluable tools for scientists studying disease mechanisms to develop new treatments for people with AVM. NINDS-funded researchers are using a newly developed adult onset mouse brain AVM model that mimics key aspects of human brain AVMs to address how loss of function of the genes Activin-like kinase (Alk1) and Endoglin (Eng) lead to HHT.

In other research projects, NINDS-funded investigators hope to develop biomarkers (signs that may indicate risk of a disease) for AVM that may improve risk assessment and aid in the choice of therapy that may provide maximize benefit with minimal risk to the individual. Additional NINDS-funded research hopes to determine molecular pathways fundamental to the formation of brain AVMs, which may lead to new therapeutic targets.

Studies of cerebral cavernous malformations (CCMs) show that alterations in the function of structural proteins may also give rise to vascular malformations. Currently there is no therapy to prevent the development or progression of CCMs. NINDS-funded scientists have developed an animal model that studies two of the familial genes related to the development of CCMs. Research shows that the protein signaling pathway Rhoa/ROCK, which allows cells to communicate regarding the formation of cell structure, is involved in blood vessel activity/the flow of molecules and cells into and out of blood vessels. These scientists hypothesize that blocking ROCK activity will inhibit CCM development and hemorrhage, and possibly create a therapy for these malformations.

In addition to NINDS, other NIH institutes and centers and support research relevant to understanding, treating, or preventing arteriovenous malformations and vascular lesions. More information is available through the NIH RePORTER (<http://projectreporter.nih.gov>), a searchable database of current and previously funded research, as well as research results and publications.

Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN

P.O. Box 5801
Bethesda, MD 20824
800-352-9424
www.ninds.nih.gov

Information also is available from the following organizations:

Brain Aneurysm Foundation

269 Hanover Street, Building 3
Hanover, MA 02339
781-826-5556
888-272-4602
www.bafound.org

**National Organization for Rare Disorders
(NORD)**

55 Kenosia Avenue
Danbury, CT 06813-1968
203-744-0100
800-999-6673 (Voicemail)
www.rarediseases.org

International RadioSurgery Association

P.O. Box 5186
Harrisburg, PA17110
717-260-9808
www.irsa.org

National Library of Medicine

National Institutes of Health
8600 Rockville Pike
Bethesda, MD 20894
301-594-5983
888-346-3656
www.nlm.nih.gov



National Institute of
Neurological Disorders
and Stroke

NIH . . . Turning Discovery Into Health

Prepared by:
Office of Communications and Public Liaison
National Institute of Neurological
Disorders and Stroke
National Institutes of Health
Department of Health and Human Services
Bethesda, Maryland 20892-2540