Classification and Endovascular Management of Pediatric Cerebral Vascular Malformations

Timo Krings, MD, PhD, FRCP(C)a,b,c,*
Sasikhan Geibprasert, MDd,e, Karel terBrugge, MD, FRCP(C)a

Before treating pediatric vascular malformation, 2 basic principles have to be taken into account that may seem trivial but still have an effect on management strategies. The first principle is that the understanding of a disease should precede its treatment. In vascular malformations, little is known about their cause, pathophysiology, or natural history, and the numerous different classification schemes that should aid in the understanding of arteriovenous (AV) shunts testify to this lack of knowledge. In addition, advances in diagnostic tools for pretreatment risk assessment as well as continuously improved treatment modalities are likely to further change the way these vascular malformations are managed. The second basic principle is that children are not small adults; vascular malformations in the pediatric population differ significantly from the adult population. Therefore, classification schemes used for and derived from the experience in treating adults are not likely to be compatible with the treatment protocols in children. As a particular example, the adult-based classification of AV shunting lesions that is related to the expected surgical outcome of AV malformations is particularly inappropriate in children, in whom (1) cerebral eloquence is difficult to assess because of the remodeling potential, particularly in the first few years of life, (2) most lesions are fistulas or multifocal, (3) the drainage usually affects the entire venous system, and (4) the potential for recovery is different. In addition, the anatomic and physiologic characteristics of the neonatal and infant brain (including hydrovenous peculiarities and immaturity of myelination) create a specific group of nonhemorrhagic symptoms and therapeutic challenges that are not encountered in adults.

KEYWORDS
- Endovascular management
- Pediatric cerebral vascular malformations • Classification
This article discusses different approaches to classifying pediatric vascular malformations and describes the endovascular management options. The difficulty in classifying pediatric cerebral vascular malformations is reflected by the large variety of different approaches that have been used for these rare diseases. These classifications may be based on symptoms, pathomechanisms, patient’s age, or morphologic features. Each of these classifications may have specific advantages, but the fact that no uniform classification has yet been decided on testifies to their specific drawbacks.

PATHOMECHANICAL CLASSIFICATION

A clinical and pathomechanical classification can lead to the following subcategories: certain high-flow shunts (ie, fistulous pial AV malformations) can lead to macrocrania, hydrocephalus, and psychomotor developmental retardation as a result of hydrovenous disorders, and cardiac insufficiency caused by cardiac overload. Venous congestion that can be caused by a high input (fistulous lesions) or a reduced outflow (secondary stenosis of the outflow pattern) may lead to cognitive decline or epilepsy. Even if signs of venous congestion are not present, a long pial course of the draining vein may indicate that venous drainage restriction is present in a large area, increasing the risk of venous congestion and subsequent epilepsy. Conversely, a short vein that drains almost directly into a dural sinus is unlikely to interfere with the normal pial drainage. If epilepsy was present in a patient with this kind of angioarchitecture, the magnetic resonance imaging (MRI) should be scrutinized for signs of perinidal gliosis or hemosiderosis as the cause of the patient’s symptoms. Mass effect is a rare pathomechanism that may result from large venous ectasias or the nidus proper compressing critical structures and may lead to epilepsy, neurologic deficits, and even hydrocephalus. Arterial steal has been associated with clinical findings such as migraine and focal deficits (fistulous pial AV malformations) or dural sinus malformations (DSMs). Systemic manifestations such as macrocrania with or without encephalomalacia (melting brain syndrome) and cardiac manifestations may be clinically present and point toward a bad prognosis. Similar to the fetal period, in the neonatal period, VGAMs, DSMs, and pial AV shunts are the predominant lesions; however, albeit rarer, cavernomas and arterial aneurysms have also been observed in this age-group. Systemic pathomechanisms as described earlier and hydrovenous pathomechanisms (hydrocephalus, maturation delay) are found more often in this period. Neurologic manifestations (seizures, focal deficits) point toward a hemorrhagic infarct or venous congestion. During infancy, VGAMs, pial AV shunts (more often fistulous than glomerular), DSMs, aneurysms, and cavernomas may be present. In shunting lesions, hydrodynamic disorders are the predominant pathomechanisms: the cerebrospinal fluid (CSF) reabsorption in this age-group is solely dependent on the venous (transparenchymal) drainage because the arachnoid granulations are not yet fully functional. Therefore, an increased pressure within the venous system (caused by an AV shunt) leads to retention of CSF within the ventricles with a concomitant increase in ventricular size and transependymal pressure gradient until a new equilibrium is found. Macrocrania, cognitive delay, hydrocephalus, and cerebellar tonsillar prolapse are the clinical manifestations at this stage.

AGE-RELATED CLASSIFICATION

A classification of pediatric vascular malformations according to the patient’s age is helpful in predicting what type of vascular malformations will be encountered, but does not explain why the predominance of specific vascular malformations in specific age-groups exists. However, the major advantage of this classification is the ability to predict symptoms that are specific for each pediatric age-group. In the fetal age, prenatal MRI or ultrasound may detect high-flow fistulous lesions, vein of Galen AV malformations (VGAMs) or dural sinus malformations (DSMs). Systemic manifestations such as macrocrania with or without encephalomalacia (melting brain syndrome) and cardiac manifestations may be clinically present and point toward a bad prognosis. Similar to the fetal period, in the neonatal period, VGAMs, DSMs, and pial AV shunts are the predominant lesions; however, albeit rarer, cavernomas and arterial aneurysms have also been observed in this age-group. Systemic pathomechanisms as described earlier and hydrovenous pathomechanisms (hydrocephalus, maturation delay) are found more often in this period. Neurologic manifestations (seizures, focal deficits) point toward a hemorrhagic infarct or venous congestion. During infancy, VGAMs, pial AV shunts (more often fistulous than glomerular), DSMs, aneurysms, and cavernomas may be present. In shunting lesions, hydrodynamic disorders are the predominant pathomechanisms: the cerebrospinal fluid (CSF) reabsorption in this age-group is solely dependent on the venous (transparenchymal) drainage because the arachnoid granulations are not yet fully functional. Therefore, an increased pressure within the venous system (caused by an AV shunt) leads to retention of CSF within the ventricles with a concomitant increase in ventricular size and transependymal pressure gradient until a new equilibrium is found. Macrocrania, cognitive delay, hydrocephalus, and cerebellar tonsillar prolapse are the clinical manifestations at this stage. After
<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>Angiographic Sign</th>
<th>Additional Imaging Diagnostics</th>
<th>Primary Pathomechanism</th>
<th>Treatment Rational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic deficits</td>
<td>Perinidal high flow and associated extranidal (remote) hypoperfusion</td>
<td>Perfusion-weighted MRI: extranidal hypoperfusion, Functional MRI (detection of eloquent tissues)</td>
<td>Steal</td>
<td>Reduce shunt</td>
</tr>
<tr>
<td>Neurologic deficits</td>
<td>Venous ectasias/pouches close to eloquent brain</td>
<td>MRI: compression, focal edema?, Functional MRI: detection of eloquent tissues</td>
<td>Mass effect</td>
<td>Remove mass effect</td>
</tr>
<tr>
<td>Headaches</td>
<td>Occipital high-flow AVM</td>
<td>Perfusion-weighted MRI: extranidal occipital hypoperfusion</td>
<td>Steal</td>
<td>Reduce shunt</td>
</tr>
<tr>
<td>Headaches</td>
<td>Large draining veins</td>
<td>MRI: hydrocephalus with draining veins close to the aqueduct or interventricular foramen</td>
<td>Mass effect</td>
<td>Decrease size of draining vein</td>
</tr>
<tr>
<td>Headaches</td>
<td>Pseudophlebitic aspect in venous phase, prolonged venous phase</td>
<td>MRI: edema</td>
<td>Venous congestion</td>
<td>Reduce shunt</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Long-standing high-flow shunts, pseudophlebitic aspect in venous phase</td>
<td>CT: calcifications</td>
<td>Venous congestion</td>
<td>Reduce shunt</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Unspecific</td>
<td>MRI: perinidal gliosis</td>
<td>Gliosis</td>
<td>Surgically removal</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Long pial course of draining vein</td>
<td>Unspecific</td>
<td>Venous restriction</td>
<td>Reduce shunt</td>
</tr>
<tr>
<td>Cardiac insufficiency</td>
<td>High-flow shunts</td>
<td>MRI/CT: large venous pouches</td>
<td>Right → left shunt</td>
<td>Reduce shunt</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>High-flow shunts, pseudophlebitic aspect in venous phase, reduced outflow</td>
<td>MRI: melting brain? CT: calcifications</td>
<td>Venous congestion in not fully matured brain</td>
<td>Reduce shunt</td>
</tr>
<tr>
<td>Dementia</td>
<td>Pseudophlebitic aspect in venous phase</td>
<td>MRI: edema</td>
<td>Venous congestion</td>
<td>Reduce shunt</td>
</tr>
</tbody>
</table>

Abbreviation: CT, computed tomography.
2 years of age, the classic AV malformations, cavernomas, aneurysms, and dural AV shunts may be encountered. Hydrodynamic pathomechanisms become less important, whereas symptoms related to the AV shunt and its secondary effects (secondary intranidal aneurysms and venous stenoses leading to hemorrhage, arterial steal, long-standing venous congestion with epilepsy, and focal neurologic deficits) are more often observed (Table 2).7

MORPHOLOGIC CLASSIFICATION

The most widely used classification of vascular malformation is based on angioarchitectural and histomorphologic features. This purely descriptive classification leads to the well-known differentiation in dural and pial AV shunting lesions, the cavernomas, capillary telangiectasias, and developmental venous anomalies (DVAs).8

To differentiate these classic types, in a first step, shunting lesions have to be discerned from nonshunting lesions, the latter being cavernomas, capillary telangiectasias, and DVAs. In a second step, within the shunting lesions, those that are supplied by arteries that would normally supply the brain or the choroid plexus (pial and choroidal brain AV malformations [AVMs]) have to be differentiated from those shunts that are supplied by arteries that normally supply the dura and meninges (ie, the classic dural AV fistulae). The nonshunting lesions, on the other hand, exhibit typical neuroimaging and histologic features that in most instances allow for a further subclassification into the cavernomas, which are composed of thin-walled, dilated capillary spaces with no intervening brain tissue and blood products in varying stages of evolution, and the capillary telangiectasias, which consist of localized collections of abnormal thin-walled vascular channels interposed between normal brain parenchyma. The DVAs are nonpathologic normal variations of the venous pattern of draining the normal brain tissue distributed along transmedullary venous anastomoses (Fig. 1).

This angio- and histoarchitectural classification is easy to implement routinely; it is able to predict the prognosis of the vascular malformation within an affected individual and is therefore of importance for the neuroradiologist and the treating physician. However, it does not help to further our knowledge or understanding of these diseases because no information about cause or the nature of the disease can be obtained from this classification. In this purely morphologic approach, secondary changes induced by the vascular malformation itself on the adjacent vasculature may be difficult to differentiate from the malformation proper. If the pathogenesis or cause are not completely understood, therapeutic approaches may therefore be difficult to tailor to an individual malformation. In addition, although rare, certain vascular malformations do not fit into any of the proposed categories, which may result in

<table>
<thead>
<tr>
<th>Age</th>
<th>Clinical Presentation</th>
<th>Type of Vascular Malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>In utero</td>
<td>Congestive cardiac failure (pulse&gt;200 beats/min, ventricular extrastoles, tricuspid insufficiency), macrocrania, ventriculomegaly, brain loss (melting brain)</td>
<td>Pial high-flow AVFs, VGAMs, DSMs</td>
</tr>
<tr>
<td>Neonate</td>
<td>Congestive cardiac failure, multiorgan failure, coagulopathies, intracranial hemorrhage (hematomas, venous infarct, SAH), convulsions</td>
<td>VGAMs, pial high-flow AVFs, DSMs</td>
</tr>
<tr>
<td>Infant</td>
<td>Hydrovenous disorders: macrocrania, hydrocephalus, convulsions, retardation, intracranial hemorrhage (hematoma, venous infarct, SAH)</td>
<td>VGAMs, pial AVMs (fistulous &gt; nidal), aneurysms, cavernomas</td>
</tr>
<tr>
<td>Child</td>
<td>Intracranial hemorrhage (hematoma, venous infarct, SAH), progressive neurocognitive and neurologic deficits, convulsions, headaches</td>
<td>Pial AVMs (nidal &gt; fistulous), aneurysms, cavernomas, dural AV shunts</td>
</tr>
</tbody>
</table>

Abbreviations: AVF, arteriovenous fistula; SAH, subarachnoid hemorrhage.
a therapeutic dilemma. Moreover, cases of transitional vascular malformations point toward a spectrum of overlapping vascular disease entities rather than clear-cut categories.

We therefore propose a classification of pediatric vascular malformations that is based on the cause of the vascular malformation to account for the shortcomings mentioned earlier. Although this classification will not alter therapeutic strategies for the time being, it may enhance our knowledge about the disease beyond its pure morphologic aspect.

ETIOLOGIC CLASSIFICATION

This classification is based on the recent understanding of angio- and vasculogenesis (on the arterial and venous side) and the influence of environmental and genetic factors. To explain the concepts of this classification, we propose 3 approaches to pediatric vascular malformations: the timing, the target, and the nature of the triggering event.

The Triggering Event

The concept of the triggering event is built on the assumption that most pediatric vascular malformations can be considered as congenital malformations (ie, malformations or structural weaknesses of the vessel that have been triggered or are present before birth and that make the vessel more prone to developing, once a second hit (or second trigger) occurs, the morphologic and/or clinical vascular lesion). This concept implies that the malformations are initially quiescent and may reveal themselves only later in life, which implies a differentiation into primary (or causative) triggers and secondary (or revealing) triggers. The stages of vascular malformations based on this assumption are therefore the prepathologic stage, during which no disease exits; however, a window of exposure opens that makes the cell temporarily vulnerable for an appropriate triggering event (eg, inflammatory, infectious, radiation-induced, toxic, metabolic, or traumatic). During the genetic stage, this appropriate (or causative) trigger for the vascular target and the time produces a primary lesion (that may result in a germinal or somatic mutation or a permanent dysfunction of the vessel). If it is neither repaired nor leads to cell death, the primary local defect (although for the time being quiescent) is transmitted to later generation cells and has a clonal remote effect. At this phase, the disease is not yet morphologically apparent, but is present as a permanent structural weakness. This stage can therefore be denominated as a biologic or premorphologic stage. Later in life (in most instances postnatal), during a new window of exposure with a secondary (or revealing) trigger, a secondary mutation or an additional dysfunction allows for the phenotypic expression of the disease. This secondary trigger may appear during repeated vascular remodeling, may be related to shear stress, inflammation or trauma, or may constitute a second (somatic) mutation. At this stage, the disease manifests itself as a morphologic but not yet clinical entity (eg, incidental finding of an

Fig. 1. Morphologic classification: these images show the classic differentiation into pial and dural AV shunting lesions (with pathologic flow voids either within the parenchyma (A) or within the subarachnoid space (B), respectively), the cavernomas with their classic mulberry shape (C), the capillary telangiectasias with the fluffy contrast enhancement (D), typically encountered in the pons), and the DVAs with their caput medusa of a dilated transmedullary vein (E).
unruptured aneurysm). This stage is the morphologic or preclinical stage. Only after failure of biologic compensation mechanisms (intrinsic repair mechanisms), or during secondary angiopathic changes (extrinsic risk factors: hemodynamic disequilibrium, shear stresses), the already morphologically fragile disease will get symptomatic and enter the clinical, symptomatic stage (Fig. 2).  

**Target of the Trigger**

Development of blood vessels from differentiating endothelial cells (EC) is called vasculogenesis, whereas sprouting of new blood vessels from the preexisting ones is termed angiogenesis. Vascular endothelial growth factor (VEGF) and its receptor VEGFR2 are the most critical drivers of embryonic vessel formation. During vasculogenesis lateral and posterior mesodermal cells migrate toward the yolk sac. During their migration, the precursors aggregate to clusters, termed hemangioblastic aggregates. The peripheral cells of these aggregates flatten to differentiate into EC, whereas the centrally located cells differentiate to hematopoietic cells of the blood islands. Following this differentiation, EC surrounding these blood islands anastomose to form a capillary meshwork, which serves as a scaffold for the beginnings of circulation, before the heart starts beating.  

It is only after the onset of heartbeat and of blood flow that the yolk sac capillary plexus is remodeled into arteries and veins in the now ongoing process of angiogenesis. Historically, it was believed that the EC of the primary capillary plexus constituted a homogenous group of cells and that further differentiation into arteries and veins occurred because of hemodynamic forces. However, in recent years, several signaling molecules were discovered, which labeled arterial or venous EC from early developmental stages onward, before the assembly of a vascular wall. Arterial EC selectively express ephrin-B2, neuropilin-1, and members of the Notch pathway, whereas other molecules are specifically expressed in the venous system only; some molecules (such as the neuropilin-2 receptor) are expressed in early stages by veins and, at later developmental stages, become restricted to lymphatic vessels. These observations led to the hypothesis that the embryonic vascular system could be predetermined to an arterial, venous, or lymphatic fate from early developmental stages onward (ie, before angiogenesis and after vasculogenesis).  

Arteries, veins, and lymphatic vessels are therefore different, molecularly defined targets. It can therefore be easily envisioned that triggering events are specific for either the arterial or the venous site. Diseases that strike only on the arterial site (aneurysms, dissections) can therefore be differentiated from diseases that are targeted against the capillary, venous, or lymphatic vessels.

**Timing of the Trigger**

The endothelium and the media of blood vessels are derived from the mesoderm and the neural crest, respectively, with the exception of the mesencephalic region and the spinal levels, both of which originate from mesoderm. These neural crest or para-axial mesoderm cells are migrating groups of cells starting from the segmented
regions. They course along predetermined paths in which daughter cells are seeded. When a defect in this migrating cell is present, the defect is transmitted to the daughter cells along its migrating path. The effect, size, area, and severity of the defect produced by the causative trigger are therefore related to the timing of the event in relation to the migration; the earlier the hit, the larger the effect on the vessels with a more widespread and severe vascular lesion. Vice versa, the later the hit, the more focal the effect and the more confined the vascular lesion. Although a germinall mutation is present in all cells, an early somatic mutation may lead to various stages of metamerically arranged defects, whereas a postnatal mutation affects only a small cluster of cells. Although congenital, some of these mutations may be revealed only later in life (such as in a failed remodeling during vascular renewal).

In the early embryonic vessel configuration (ie, during the early stages of angiogenesis and after the heart started beating) not all capillaries are integrated into the primitive circulation. In this period, the primitive circulation consists of direct transitions of arteries into veins; arterial and venous blood can flow through the same vascular channel. This embryonic circulation is therefore different from the adult situation (in which blood flows through arteries into arterioles, a capillary bed, and through successively larger veins back to the heart). If this embryonic arterial-venous vessel configuration persists, large arterial-venous shunts will develop (which may be the case in certain fistulous malformations of the brain and spine). With further development of the vasculature (ie, in later embryonic and fetal stages), the area of the shunt may become more confined, again revealing the importance of the timing of the triggering event in relation to the size and effect of the vascular malformation.

**Nature of the Trigger**

Depending on the type of trigger, purely genetic diseases (such as hereditary hemorrhagic telangiectasia [HHT]) can be differentiated from purely extrinsic diseases (such as vascular traumatic lesions). In between these extremes, however, triggering events with varying roles of genetic and environmental triggers can be identified.

This concept leads to the classification shown in Table 3, in which focal, segmental, and metameric lesions (which depend on the timing of the triggering event) are tabulated against the location of the lesion along the arteriocapillary-venous tree (as the specific target hit by the triggering event) and the nature of the trigger (ie, genetic vs nongenetic). Thus, the following classification of pediatric vascular malformations is proposed, keeping in mind that this classification has to be regarded as a spectrum of diseases and that the subclassifications presented constitute arbitrary boundaries.

**MANAGEMENT STRATEGIES FOR PEDIATRIC VASCULAR MALFORMATIONS ACCORDING TO THE ETIOLOGIC CLASSIFICATION**

**Arterial Lesions**

**Focal arterial lesions**

On the arterial side, aneurysms and arterial dissections are those vascular lesions that are caused by a focal effect on the arterial tree. They can be related to genetic influences (such as in arterial aneurysms associated with neurofibromatosis type 1, Ehlers-Danlos syndrome type IV, and familial immune deficiency syndrome) or to purely

---

**Table 3**

The etiologic classification of pediatric vascular malformations based on the timing, the target, and the nature of the triggering event (diseases in italics denominate a purely genetic nature of the trigger)

<table>
<thead>
<tr>
<th>Target</th>
<th>Late Hit → Focal Disease</th>
<th>Intermediate Hit → Segmental Disease</th>
<th>Early Hit → Metameric Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial level</td>
<td>Aneurysms, arterial dissections, <em>Ehler-Danlos syndrome IV</em>,<em>Marfan syndrome, NFI</em></td>
<td>Mirror (twin) aneurysms and dissections, segmental aneurysm</td>
<td>PHACES</td>
</tr>
<tr>
<td>AV level</td>
<td>AVM, VGAM, <em>HHT</em></td>
<td>Proliferative angiopathy</td>
<td>CAMS</td>
</tr>
<tr>
<td>Venous level</td>
<td>DVAs, sinus pericranii, cavernoma, <em>familial cavernomas</em></td>
<td>DSM</td>
<td>Cerebrofacial venous metameric syndrome, <em>blue rubber bleb nevus</em></td>
</tr>
</tbody>
</table>
environmental factors (such as vascular trauma). Presumably most arterial aneurysms and dissections in the pediatric age-group are related to environmental and genetic influences with intrinsic predisposing factors such as segmental vulnerability, wall matrix failure, and altered repair mechanisms on the one hand, and extrinsic triggering factors such as inflammation, (minor) trauma, and autoimmune-related causes on the other (Fig. 3).16,17 Although the complete description of treatment strategies in pediatric aneurysms is beyond the scope of this article, their (dissecting, traumatic, or infectious) nature often leads to the necessity of parent vessel occlusion with the risk of subsequent stroke. Because the disease process (given its cause) is in most cases located in the vessel wall, a purely endoluminal treatment (ie, coiling of the aneurysm) is successful only in patients in whom true saccular aneurysms are present. Most aneurysms, however, are a symptom rather than the disease itself and therefore require a more thorough evaluation of their cause before treatment (Fig. 4).

Segmental arterial lesions
Mirror or twin aneurysms and the rarely occurring segmental aneurysms belong in this group.16,19 Mirror aneurysms are aneurysms that occur on identical vascular segments bilaterally and may be related to vascular precursor cells that originate from a mother cell whose clones migrated to the same vessel segment within both hemispheres. These cells have been identified in quail-chicken chimera experiments and point toward a defect that occurred earlier during vasculogenesis and therefore affects a larger portion of the arterial tree (Fig. 5).20 The association of cervical internal carotid artery (ICA) aneurysm with ipsilateral vertebobasilar aneurysm is grouped in the same category. The association of a developmental error being expressed in two seemingly separate segments that are linked (from a phylogenetic and embryologic point of view) by the hypoglossal artery suggests a segmental error related to this embryonic vessel.21 Treatment strategies in these aneurysms are similar, as discussed in the previous section; however, the treating physician

Fig. 3. Aneurysms and dissections can be regarded as focal arterial lesions. Here, 2 pediatric patients with an inflammatory aneurysm of the distal fronto-opercular branch of the middle cerebral artery (upper row) and a dissecting aneurysm of the left middle cerebral artery are shown.

Fig. 4. Segmental arterial lesions.
has to keep in mind that the vessel wall in the affected segment may be congenitally weakened and may therefore lead to future recurrences, necessitating close imaging follow-up.

**Metameric arterial lesions**

When the mesodermal cells migrate to their target organs, they seed daughter cells along their predetermined paths. Once these daughter cells have migrated to their target organ, they may acquire phenotypic specificity as a result of cell-cell signaling. A defect in one of these early mesodermal cells may lead to longitudinally arranged or metameric syndromes, with multiple phenotypic expressions along the migration paths. This may lead to the occurrence of seemingly unrelated (and mostly arterial) lesions, grouped according to the acronym PHACES: posterior fossa malformations, hemangiomas, arterial malformation (including the aorta and the cranial vessels with dolichosegments and stenoses), cardiac defects, eye abnormalities, and sterna raphe defects (Fig. 6). Treatment of PHACES syndrome should be symptomatic and, for the hemangiomas, treatment strategies should not differ from those used for the nonsyndromal forms. With respect to the arterial anomalies, segmental dysplasias or dolichosegments do not constitute entities that should be treated and should not be misdiagnosed for AV malformations or aneurysms.

**Capillary Lesions (ie, Lesions at the AV Junction)**

**Focal capillary lesions**

A focal lesion at the AV junction may produce a shunt that can be pial, dural, or choroidal, leading to the classic AVMs, choroidal AVMs...
(such as the classic VGAMs), or to dural AV shunts. These focal AV lesions may be related to a purely genetic disease (such as HHT) and encompass a spectrum of diseases: from shunting lesions with a large volume (ie, a large opening of the artery into the vein, which is, given the considerations on the timing of the event mentioned earlier, most likely related to an early causative trigger) to microshunts, and from extended shunting zones (holohemispheric AVMs) to localized nidi (Fig. 7). Treatment strategies in these lesions are complex and related to the individual clinical presentation and AVM angioarchitecture. At least 3 different groups of patients have to be distinguished: asymptomatic patients, nonhemorrhagic symptomatic patients, and patients who became symptomatic as a result of an intracranial hemorrhage. However, in all 3 groups a careful analysis of the angioarchitecture is necessary (1) to predict further hemorrhagic and nonhemorrhagic deficits, (2) to evaluate whether the specific symptoms of an individual patient can be related to the AVM, and (3) to define the point of rupture. This analysis of the angioarchitecture not only enables

Fig. 6. Metameric arterial vascular lesion. In this 8-year-old girl, a right-sided facial hemangioma, a posterior fossa malformation, and dolichoectatic ICAs are present.

Fig. 7. Focal AV (or capillary lesions) are present in the nidal AV malformations (right panel) but also in the fistulous AV malformations (middle panel) or in the VGAMs as a special form of pediatric choroidal AV malformation.
classification according to the pathomechanical classification as pointed out in Table 1 but also relates to future hemorrhagic risks by evaluating focal weak points. These angioarchitectural weak points are (1) intranidal aneurysms and venous ectasias and (2) venous stenosis.

The first investigators to state that specific angioarchitecture present in brain AV malformations make them more prone for future hemorrhage were Brown and colleagues in 1988, who found that the annual risk of future hemorrhage was 3% in brain AVMs alone, and 7% per year in brain AVMs (B-AVMs) with associated pre- and intranidal aneurysms.

Meisel and colleagues found that among 662 patients with B-AVMs there were 305 patients with associated aneurysms and there was a significant increase in rebleed episodes in B-AVMs harboring intranidal aneurysms (P < .002). In the Toronto series of 759 B-AVMs, associated aneurysms were statistically significantly (P = .015) associated with future bleeding (Fig. 8). It may be difficult to discern intranidal arterial aneurysms from intranidal venous ectasias, which is why these 2 angioarchitectural specificities are grouped as 1 entity in most series. Venous stenoses, on the other hand, are a separate angiographic weak point and are often seen in ruptured AVMs. The nature of the venous stenosis is not completely understood; high-flow vessel wall changes, failure in remodeling, or an increased vessel wall response to the shear stress induced by the arterialization have been proposed as potential causes. A stenotic venous outlet leads to an imbalance of pressure in various compartments of the AVM, which may induce subsequent rupture of the AVM. The compartment that is drained by the stenotic vessel should be scrutinized for contrast stagnation and, if endovascular therapy is contemplated, extreme caution has to be undertaken not to push liquid embolic agent toward the already stenosed vein, as this may lead to catastrophic results. In addition to these 2 angioarchitectural risk factors, other factors may lead to an increased risk of hemorrhage; these are deep venous drainage only, older age, and male gender.

Analysis of the angioarchitecture has to be performed before contemplating therapy for an AVM; specifically, the following points have to be addressed: the nature and number of the feeding arteries, the presence or absence of flow-related aneurysms; the number of separate compartments of the malformation; any arterial or venous ectasias.

Fig. 8. In patients with AVMs, associated aneurysms should be considered as the source of bleeding.
near to or within the malformation; and the nature of the venous drainage (Table 4). On the arterial side, flow-related aneurysms (discussed in greater detail later) are typically present on branching points of the major feeding arteries. They classically resolve following treatment of the AVM and are caused by vascular remodeling following increased shear stress. Although not a contraindication for endovascular treatment, they present a danger to the neurointerventionalist, because flow-directed catheters are prone to enter the aneurysm rather than the distal vessels. Concerning the arterial side of the AVM, the number and the nature of the feeding arteries need to be assessed because they determine whether endovascular approaches make sense. A large number of only slightly dilated feeders make an endovascular therapy more challenging than those with a single large feeder. Two basic types of feeding arteries may be encountered. Direct arterial feeders end in the AVM, while indirect arterial feeders supply the normal cortex and also supply the AVM en passage via small vessels that arise from the normal artery (Fig. 9).

Whereas direct feeders are safe targets for an endovascular therapy, en passage feeders may carry the risk of inadvertent arterial glue migration to distal healthy vessels. In this regard, the security margin of the catheter position has to be briefly discussed. Liquid embolic agents may cause reflux at the end of the injection. Depending on the agent, the microcatheter, the injection technique, and the skills of the operator, this reflux may be as far as 1 cm proximal to the tip of the catheter. A safe deposition of liquid embolic agent is therefore possible only if the catheter tip is distal enough to be beyond any vessel that supplies normal brain tissue. In AVMs with en passage feeders, this may not be possible, especially if the catheter is only hooked into the feeding artery and jumps backward because of the jet effect when liquid embolic agent is injected.

Moving from the artery to the angioarchitecture of the nidus, intranidal arterial aneurysms and venous varices that indicate weak points need to be recognized as well as the number of compartments and their nature (nidal vs fistulous) (Fig. 10). On the venous side of the AVM, the number of draining veins per compartment (the more the better for endovascular treatment if venous migration occurs), possible drainage into the deep venous system (higher risk for hemorrhage, more difficult surgical treatment), and stenosis that restrict venous outflow have to be identified to fully determine the risk of a specific AVM. This information can be obtained only by conventional digital subtraction angiography, which in our practice must still precede any treatment decision in AVMs.

Table 4

Features important for a treatment-based classification of B-AVMs using endovascular techniques

<table>
<thead>
<tr>
<th>Artery</th>
<th>Flow-related aneurysms</th>
<th>Number of feeder</th>
<th>Type of feeder (direct vs en passage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nidus</td>
<td>Number of compartments</td>
<td>Intranidal aneurysms</td>
<td>Fistulous versus nidal</td>
</tr>
<tr>
<td>Veins</td>
<td>Stenoses</td>
<td>Number of draining veins per compartment</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 9. Indirect versus direct feeder in 2 AVMs: the pericallosal AVM is supplied by a multitude of indirect feeders, whereas the postcentral AVM is supplied by a single-terminal direct feeder and therefore is more amenable for embolization.
A complete cure of a pial brain AVM by endovascular means is possible in approximately 20% of all AVMs irrespective of their angioarchitecture. Those AVMs that are favorable to a complete cure are the small, single-feeder, single-compartment AVMs that have a direct feeding artery. Because these AVMs are also good candidates for radiosurgery and open neurosurgery, a tailored team approach is preferable for each specific AVM in each individual patient, respecting their wishes and taking into consideration the clinical presentation. In most instances, endovascular therapies are used to diminish the size of an AVM before radiotherapy or surgery, to secure focal weak points in the acute and subacute stage of ruptured AVMs (Fig. 11) and in unruptured AVMs in which radiosurgery is contemplated, or to exclude those compartments of an AVM that may be difficult to reach during surgery. Once treatment for an AVM is decided upon, a pathway to its complete exclusion has to be agreed on by the treatment team, which should include radiosurgeons, vascular neurosurgeons, and neurointerventionalists. It does not make sense in our opinion to partially treat an AVM without a strategy on how to handle a possible residual of the AVM.

If endovascular therapy is chosen, we proceed with a predefined goal, which may mean performing what has been termed a partially targeted embolization. Such rationale is based on the outcome of a series of more than 600 patients with AVMs who were partially embolized and showed a significant decrease in hemorrhage episodes when compared with the conservatively treated series reported in the literature. The
yearly hemorrhage incidence rate of patients before partial treatment was 0.062 (95% confidence interval [CI] 0.03–0.11). The observed annual rate after the start of this regime was 0.02 (95% CI 0.012–0.030).\(^3^8\) Given the considerations mentioned earlier concerning focal weak points, we think that these numbers reflect the benefit of selectively embolizing specific weak compartments of an AVM, thereby providing early protection while the patient is scheduled for radiotherapy (the effects of which take more time but with higher rates of complete obliteration). In these instances the goal is to secure the AVM during the waiting period for complete occlusion. In other instances the goal may be to exclude those compartments that are difficult to reach before surgery or to diminish the size of the AVM before radiosurgery. In the latter instances, compartments in the periphery of the AVM have to be targeted, whereas in the former instances, the neurosurgeon has to point out the target to the neurointerventionalist. In combined therapies (endovascular + radiotherapy; endovascular + surgery) the relative risks of each procedure are cumulative, and embolization makes sense only if a goal is predefined before the therapy. In most instances, this goal should be reached after a maximum of 2 to 3 endovascular sessions.

For most pial AVMs, liquid embolic materials are the first choice of treatment. The therapy is performed under general monitored neuroanesthesia. We classically use a 5-F guiding catheter that is placed into the distal ICA or vertebral artery. A flow-directed microcatheter is then advanced and directed with a microguidewire or gentle contrast injections into the feeding artery and into the nidus proper using roadmap or fluoroscopy techniques. Here a wedged position of the catheter tip is sought, paying careful attention to avoid venous migration. Depending on the type of embolic agent and the nidus (fistulous vs nidal), the injection techniques vary. To prevent venous migration, the blood pressure may be temporarily lowered, or the jugular veins may be compressed. There is an ongoing debate into what kind of liquid embolic agent to use. Personal experience of the authors as well as published data show a higher rate of complete obliteration with the use of Onyx (40%–60%) but with a significant increased treatment associated risk for permanent morbidity and mortality (8%–12%).\(^3^9,4^0\) Proximal occlusion of feeding arteries without penetration of the embolic material to and just beyond the site of the shunt reopens the nidus via leptomeningeal collaterals and may induce a profound neoangiogenesis, which should be avoided because subsequent endovascular therapies will not be possible. In addition, the profound neoangiogenesis makes discrimination between the nidus proper and normal brain supplying arteries nearly impossible. Therefore, in the opinion of the authors, coils and microcoils are not indicated for nidal type AVMs. These embolization materials have a place only in certain single-hole macrofistulae. Likewise, particles, especially if too large, may lead to an occlusion that is too proximal with subsequent neoangiogenesis. In addition, particles do not result in a stable occlusion in pial brain AVMs and their use at the end of a procedure is more cosmetic.

Although most AVMs have both fistulous (ie, direct transitions of arteries and veins) and glomerular (ie, shunts with an intervening network of pathologic vessels) compartments, a specific subset of purely fistulous pial AV shunts, called the pial single-hole macrofistulae, deserve special consideration. They are often present in children and should raise the suspicion of an underlying genetic disease such as HHT.\(^1^4\) HHT is inherited as an autosomal-dominant trait, with varying penetrance and expressivity. Cerebral pial AV fistulas in HHT are macrofistulae with a high
fistula volume and are of the single-hole type. The feeding arteries drain directly into a massively enlarged venous pouch and often there is only 1 single-feeding artery. Signs of venous congestion are typically present because of venous overload and are responsible for the patient’s symptoms. Associated angiographic abnormalities include venous ectasias, venous stenoses, pial reflux, venous ischemia, calcifications, and associated arterial aneurysms. Patients are typically younger than 16 years and there is a propensity for early infancy (in our series all patients but 2 were less than 6 years old). Localization of the arteriovenous fistula is either cortical supratentorial or infratentorial and deep locations are exceptional. Presenting symptoms are intracerebral hemorrhage in most patients; macrocrania, bruit, cognitive deficits, cardiac insufficiency, epilepsy, tonsillar prolapse, and hydrocephalus may also be present.

In our practice, treatment consists of superselective glue embolization to obliterate the fistulous area by pushing the glue via the artery into the venous pouch to establish a mushroom-shaped glue cast that occludes the single-hole fistula. Alternatively, coils may be used to selectively occlude the fistulous site. Because a major problem of glue embolization is the uncontrollable propagation of glue into veins with secondary venous occlusion and hemorrhage, we try to minimize this risk in these macrofistulae by using undiluted glue with tantalum powder at a position close to the venous pouch with the catheter tip pointed against the vessel wall. In selected patients flow reduction with coils may be used before glue embolization (Fig. 12).

**Segmental capillary lesions**

The disease entity of proliferative angiopathy can be placed on the segmental side of the spectrum.

---

**Fig. 12.** Macrofistula in a child with HHT in whom as a first step, the flow was reduced by transarterial coiling of the venous pouch, followed by injection of pure glue to completely occlude the fistula.
of lesions at the AV junction (Fig. 13). This vascular lesion can be regarded as separate from classic brain AVMs in angioarchitecture, natural history, clinical presentation, and, therefore, treatment. Instead of a compact or focal nidus, often multiple lobes or even a whole hemisphere are affected by a diffuse network of spaces with intermingled normal brain parenchyma. The discrepancy between the large nidus and the small shunting volume, the absence of flow-related aneurysms, the presence of diffuse angiogenesis (eg, transdural supply, progressive arterial occlusion), and the small caliber of a multitude of feeding arteries and draining veins are the angiographic hallmarks of this disease and point toward a diffuse angiogenetic activity. This activity is presumably related to reduced perinidal perfusion and subsequent chronic cortical ischemia. Concerning treatment strategies, surgery, radiotherapy, or nontargeted embolization of most of the malformation carry the risk of permanent neurologic deficit because of the interspersed normal neural tissue. This disease does not carry a high risk of hemorrhage; instead one of the major pathomechanisms of this disease is ischemia (which is probably multifactorial as a result of incompetent angiogenesis, steal phenomena, arterial stenosis, and capillary wall involvement). Therefore, a therapy that enhances cortical blood supply (such as calvarial burrholes) may be indicated. Similar to moyamoya-like diseases these burrholes increase the cortical blood supply by recruiting additional dural blood supply. If patients present with hemorrhage, however, endovascular treatment should be performed and aimed at fragile areas that may be identified during angiography.

**Metameric capillary lesions**

The association of AV malformations of the brain, the orbit (retinal and/or retrobulbar lesions), and the maxillofacial region was originally named after Bonnet-Dechaume-Blanc and Wyburn-Mason. Given the considerations mentioned earlier about

---

**Fig. 13.** Segmental AV lesions are those vascular malformations of the capillary level that have an extensive involvement of more than 1 lobe, or sometimes, the whole hemisphere. Proliferative angiopathy is the classic disease entity of this group.

**Fig. 14.** The association of a corpus callosum AVM and a vascular malformation of the tip of the nose constitutes the midline prosencephalic type of a CAMS as a metameric AV vascular malformation.
the timing and the triggering of vascular malformations and our knowledge about the specific predetermined migration patterns of cells, it became clear that the association of different forms of AVMs follows a specific pattern that allows differentiation of different cerebrofacial AV metameric syndromes (CAMS). CAMS 1 is a midline prosencephalic (olfactory) group with involvement of the hypothalamus, corpus callosum, hypophysis, and nose; CAMS 2 is a lateral prosencephalic (optic) group with involvement of the optic nerve, retina, parietotemporal-occipital lobes, thalamus, and maxilla, and CAMS 3 is a rhombencephalic (otic) group, with involvement of the cerebellum, pons, petrous bone, and mandible. The insult producing the underlying lesion develops before the migration occurs and thus before the fourth week of development. The disease spectrum may be incomplete or metachronous (Fig. 14). Given their large size, and their potential to grow, treatment of these lesions is likely to be palliative and in our experience indicated only to focus on locally fragile areas (such as intranidal aneurysms, large shunts, compartments with venous outlet restrictions).

**Venous Lesions**

**Focal venous lesions**

In this category belong vascular malformations and variations as diverse as sinus pericranii, DVAs, and cavernomas. Genetic forms of this category are known and present as the familial form of cavernomas, with at least 3 different gene loci identified (Fig. 15). These vascular malformations, although seemingly unrelated, share a defective or malformative focal development of the venous system. Transitions and combined vascular malformations exist such as a DVA draining through a sinus pericranii, a cavernoma related to a DVA, or even a true AVM draining via a DVA, underlining that this classification is a spectrum of overlapping malformations, vascular lesions, and diseases. An endovascular therapy is either not possible (such as in cavernomas) or
contraindicated (such as in most DVAs and sinus pericranii given their role in the drainage of the brain).

**Segmental venous lesions**
If the venous lesion affects a larger cluster of cells, more severe venous defects are encountered. The classic example is DSMs,\(^4^9\) in which the development of the dural sinuses is affected (Fig. 16). This disease leads not only to sinus wall overgrowth and epidural confluences of venous spaces with giant lakes but also to cavernomas, sinus pericranii, DVAs, and maxillofacial malformations. The AV shunts associated with DSM add to the venous congestion of the normal brain.\(^5^0\) Therefore treatment is targeted toward reduction of the shunt via a transarterial approach.

**Metameric venous lesions**
The encephalotrigeminal angiomatosis or Sturge-Weber syndrome is a nonfamilial disease with a skin discoloration (port wine) in the V\(_1\) territory associated with a calcified leptomeningeal venous malformation of the ipsilateral supratentorial hemisphere, which (in relation to the CAMS mentioned earlier) may be termed cerebrofacial venous metameric syndrome.\(^1^1\) Associated with the classic facial portwine stain are intracranial vascular anomalies that consist of cortical venous thrombosis with capillary venous proliferation and enlargement of the transmedullary collateral venous drainage with or without choroid plexus hypertrophy (Fig. 17). A genetic disease that falls into the metameric venous lesion group is the blue rubber bleb nevus syndrome, which involves multiple venous lesions (such as DVAs).\(^5^1\) Endovascular therapies are not established for these diseases.

**SUMMARY**
The proposed classification may add to our understanding of vascular malformations because the phenotypic expression of a given vascular disease can shed light on the nature and timing of the triggering event, thereby potentially opening up treatment modalities that are directed against the triggering event rather than against the clinical manifestations or the morphologic appearance. In addition, the proposed classification may shed light on the prognosis and pathomechanisms of certain vascular malformations and may, therefore, lead to better treatment of the child afflicted with these rare and difficult diseases. For the time being, treatment in many instances is still related only to the symptoms of the disease, not to the disease process itself. However, with the methods at hand, most vascular diseases can nowadays be approached safely and with good clinical results.

**REFERENCES**
4. Hademenos GJ, Massoud TF. Risk of intracranial arteriovenous malformation rupture due to venous...


