The neurovascular triad: mixed cavernous, capillary, and venous malformations of the brainstem

EUGENIO POZZATI, M.D.,1 ANNA FEDERICA MARLIANI, M.D.,1 MINO ZUCCHELLI, M.D.,1 MARIA PIA FOSCHINI, M.D.,1 MASSIMO DALL’OLIO, M.D.,1 AND GIUSEPPE LANZINO, M.D.2

1Department of Neurosurgery, Sections of Neuroradiology and Pathology, Bellaria Hospital, Bologna, Italy; and 2Department of Neurosurgery, Illinois Neurological Institute, University of Illinois College of Medicine, Peoria, Illinois

Object. The four types of cerebrovascular malformations may sometimes be combined and more often occur in pairs; triads are exceptional. The authors present six patients with the clinicoradiographic profile of mixed vascular malformations of the brainstem, including cavernous malformation (CM), capillary telangiectasia, and developmental venous anomaly (DVA).

Methods. Five patients (one of whom was a child) suffered from hemorrhage, suggesting that this complex association has a high bleeding potential. Progressive growth, rebleeding, and de novo occurrence of the associated CM were documented in three cases. Magnetic resonance imaging of the brain was obtained in all patients by using one or more of the following modalities: T1-weighted sequences before and after gadolinium administration; T2-weighted sequences; T2-weighted fluid attenuated inversion recovery; T1-weighted fast spin echo; and diffusion weighted, diffusion tensor, and perfusion imaging in three cases.

Results. Three patients were surgically treated with the intention of excising the hemorrhagic lesion, but only two patients had their malformations successfully removed. In the third case, diffuse pontine telangiectasia precluded the safe excision of the CM. Histological examination demonstrated a blended pathological milieu characterized by coalescent telangiectasia and venules associated with loculated endothelial chambers resembling an immature or de novo CM. Three patients were treated conservatively; recurrent minor hemorrhage occurred in one case. The authors found these malformations to be arranged in two basic relationships: CM inside the telangiectasia and CM in the radicles of the DVA. Stenosis of the main venous collector and dilation of the medullary veins were important findings.

Conclusions. The pathogenesis of this malformation may be referred to a developmental deviance of the brainstem capillary–venous network associated with transitional vessels and loculated endothelial vascular spaces related to genetic and acquired origins, probably in a restrictive venous outflow milieu. (DOI: 10.3171/JNS-07/12/1113)

KEY WORDS • brainstem • cavernous malformation • magnetic resonance • mixed vascular malformation • telangiectasia • venous angioma

INTERRACRANIAL vascular malformations classically include the following four types: arteriovenous malformation, CM, capillary malformation (or telangiectasia), and DVA or venous angioma. These vascular malformations are often solitary. Nevertheless, so-called mixed malformations occurring in pairs1,2,5,26 or, exceptionally, in triads10 have been increasingly recognized. Among nonarterial vascular malformations, the most frequent association is observed between CM and DVA, although telangiectasias associated with DVAs or CMs have also been reported.1,2,12,19 The only report of juxtaposition of a triad composed of CM, DVA, and telangiectasia in the brainstem was described by Clatterbuck et al.10 A detailed description of the neuroimaging, clinical, and histopathological characteristics of this triad can be helpful in furthering our understanding of the genesis and behavior of these malformations. We describe a series of patients with the CM-DVA-telangiectasia triad occurring at a consistent pontine location in a variable mosaic related to developmental and acquired alterations of the capillary–venous circulation.

Illustrative Cases

Case 1

This 14-year-old boy was admitted with headache, vomiting, and gait disturbance. A CT scan demonstrated hem-
orrhage in the right cerebellar peduncle and pons. Admission MR imaging demonstrated a multiloculated hemorrhage consistent with a CM. Following administration of contrast medium, a large pontine telangiectasia and a DVA also became apparent on FSE images (Fig. 1a–e). Cerebral angiography confirmed a pontine DVA but no other anomalous findings. The lesion was resected through a suboccipital craniectomy via the subtonsillar approach. Macroscopically, the malformation had the appearance of an angiomatic hemorrhagic nodule. Histopathological studies demonstrated telangiectasia and venules associated with multiloculated endothelial spaces characteristic of a CM (Fig. 2). Postoperatively, the patient suffered diplopia, facial hypesthesia, and gait ataxia, which resolved completely within 1 month. Follow-up MR imaging confirmed total removal of the hemorrhagic CM (Fig. 1f), with no changes in the appearance of the telangiectasia and the DVA.

Case 2

This 43-year-old man presented in 1999 with headache, diplopia, and gait imbalance. An MR imaging study revealed a CM under the floor of the fourth ventricle associated with a DVA draining through the lateral recesses. Gadolinium administration revealed a telangiectasia of the pons. Surgical exploration was conducted via a transvermian approach and revealed a DVA and speckled hemorrhagic lesions (representing telangiectasia) throughout the floor of the fourth ventricle without a clearly emerging CM. These vascular findings precluded safe removal of the underlying CM, and the procedure was aborted. The patient was discharged without additional deficits. Two years later, after strenuous physical exertion, he suffered recurrent headache, left facial paresis, and diplopia. A repeated MR imaging study demonstrated an increase in the size of the CM, with evidence of recent intralesional hemorrhage. The study once again confirmed the adjacent known DVA and pontine telangiectasia. No further treatment was recommended. The facial paresis and diplopia gradually subsided and he remains in good clinical condition without clinical recurrence.

Case 3

This 81-year-old woman with history of hypertension was admitted with a chief complaint of occipital headache and left facial paresthesia. A CT scan revealed a small pontine hemorrhage. The patient underwent catheter angiography, which showed abnormal veins in the vicinity of the hemorrhage detected on CT scanning. A brain MR imaging study disclosed a small CM, a DVA with the typical caput medusae appearance, and diffuse contrast enhancement in the pons consistent with telangiectasia. The hemorrhage was managed conservatively and the patient experienced progressive partial improvement of her facial paresthesia with no clinical recurrences at follow-up evaluation.

Case 4

This 29-year-old woman presented with acute onset of left facial paresthesia and dysmetria 4 weeks after giving birth (the delivery was uncomplicated). A CT scan of the brain revealed a small calcification in the pons underneath the floor of the fourth ventricle. Admission MR imaging revealed a hypointense pontine lesion consistent with a partially calcified CM and a venous anomaly draining into the left lateral recess of the fourth ventricle. After contrast administration, a diffuse pontine telangiectasia surrounding the CM was evident (Fig. 3). Her neurological disturbances gradually subsided, and follow-up MR images obtained 3 and 12 months later confirmed the typical neuroimaging findings of the three vascular malformations (Fig. 4 left) and additional enlargement of the venous radicles in the fourth ventricle (Fig. 4 right).

Case 5

This 35-year-old woman presented in 1999 for evaluation of a recent onset of double vision. Her medical history was consistent with a transient episode of diplopia in 1982 at the age of 12 years. At that time, CT scans of the brain had not revealed a lesion. A CT scan of the brain obtained after her admission in 1999 revealed hemorrhage in the pontine tegmentum. An MR image demonstrated a mixed-signal-intensity lesion surrounded by a hypointense rim, which was consistent with a CM. After gadolinium administration, a complex vascular malformation characterized by a DVA with multiple drainage channels through the pons and ventricular floor associated with a pontine telangiectasia (Fig. 5) became apparent. The patient’s symptoms gradually improved and she was discharged home. She remained in good clinical condition until December 2005, when she complained of recurrent diplopia; a CT scan demonstrated a small hemorrhage in the pons. An MR image confirmed the same vascular lesion, which was grossly unchanged in its morphology. No therapy was recommended. At her 6-month follow-up visit she remained clinically stable with no recurrence but with some residual diplopia.

Case 6

This 21-year-old man presented with acute occipital headache, vertigo, and gait imbalance. A CT scan showed a pontine hemorrhage, and MR imaging revealed a heterogeneous hemorrhagic lesion consistent with a CM abutting the ventral pontine surface and cradled in a large DVA. Following administration of contrast medium, enhancement of the surrounding pons in a pattern consistent with capillary telangiectasia was also seen. A suboccipital craniectomy was performed, and a hemorrhagic nodule was excised from the right pons through a lateral transpontine access. The patient’s postoperative course was uneventful. Histological examination revealed a mixed vascular malformation composed of coalescent telangiectasia and venules associated with closely packed endothelial vascular spaces, consistent with a CM. Postoperative MR imaging confirmed complete excision of the pontine vascular malformation and the intact large DVA characterized by a segmental stenosis in its main venous collector draining into the superior petrosal sinus (Fig. 6). Follow-up MR images obtained 1 year later demonstrated dilation of the venous radicles of the DVA associated with a minute de novo CM (Fig. 7).

Discussion

Cerebrovascular malformations in mixed forms have...
been recognized for some time. The association between CMs and DVAs has received particular attention and has triggered speculation about a reciprocal causal relationship between these lesions. Recently, Clatterbuck and coworkers\textsuperscript{10} reported the association of CM, DVA, and telangiectasia in the pons. Their description was purely clinical and radiological without histological confirmation.\textsuperscript{6} Over the years, we have encountered six patients with this neurovascular triad. The possible origin of this association is intriguing, as are the pathological and neuroimaging aspects, the clinical significance, and the reciprocal relationships of telangiectasia, DVA, and atypical CMs.

**Lesion Types**

**Telangiectasia.** Cavernous malformations and telangiectasias (with the rare thrombosed or cryptic arteriovenous malformations) traditionally belong to the group of angiographically occult vascular malformations.\textsuperscript{29,30} Telangiectasia is considered congenital and generally occurs in the pons, with possible extension into the middle cerebellar peduncles.\textsuperscript{5,7,15,16,18} The typical pathological appearance is that of dilated capillary spaces interspersed in the normal parenchyma. The occasional association with enlarged draining venous vessels has led some authors to suggest the existence of transitional capillary–venous malformations, which might be acquired rather than congenital, because of the obstructed venous outflow.\textsuperscript{15,18,24} Telangiectasia is generally diagnosed in adults, and reports in pediatric patients, as in Case 1, are unusual.\textsuperscript{5,15,18}

Telangiectasia usually exhibits a benign clinical course; however, some reports indicate a more aggressive evolution due to chronic ischemic injury, hemorrhage, or other local damage.\textsuperscript{28} In spite of considerable variability, diagnosis is possible with MR imaging, which demonstrates slight, varying hyperintensity on T2-weighted images, contrast enhancement, and gradient recalled echo signal loss related to the presence of deoxyhemoglobin in the slow-
flowing blood. These MR features may not be fully sensitive due to the different density and flow conditions of the capillaries, with areas of stagnant circulation, which may correlate to oval-shaped regions of low signal intensity depending on occasional venous restriction. This flow change may favor intraluminal thrombosis and trigger a cavernomatous conversion with elusive radiological evidence related to the unusual interface and intermingling of the two malformations. In our six cases, telangiectasia did not manifest as an abnormality on T1-weighted sequences, demonstrated hyperintensity on T2-weighted sequences in four cases, was associated with contrast enhancement in all cases, and resulted in a low-intensity signal on gradient recalled echo sequences only in half the cases.

Cavernous Malformations and Telangiectasia. The distinctive pathological element of CMs consists of closely packed vascular channels lined by endothelial cells: dense connective matrix, thrombosis, calcifications, hemosiderin deposition, and peripheral gliosis constitute the usual findings in the “mature” lesion. Telangiectasia and CMs are considered to be the two opposite ends of a spectrum; they display apparently identical component vessels and are distinguished by the presence or absence of intervening neural tissue. “Incompetency” of the vascular wall due to disruption of interendothelial connections is the main pathophysiological element differentiating a CM from a telangiectasia. Cavernous malformations may be familial and sporadic, the latter being also congenital or acquired. Sporadically novo CMs may occur after brain irradiation; as a complication of a preexisting DVA; or as a novel, non-inherited mutation in the KRIT1 gene. Unlike DVA and telangiectasia, overt hemorrhage represents a distinctive clinical manifestation of CMs.

Developmental Venous Anomalies. Developmental venous anomalies are thought to be congenital and consist of a star cluster venous system collecting in a deep draining vein; they are usually angiographically evident in the form of the classic caput medusae. Their hemorrhagic risk is negligible, but a DVA draining through the brainstem into

**Fig. 3.** Case 4. Axial CT scan (a) demonstrating a calcification in the pons. Axial fluid attenuated inversion recovery T1-weighted (b) and FSE T2-weighted (c) MR imaging studies demonstrating gradations of hypointensity due to hemosiderin deposition consistent with a CM around the calcification. Axial (d) and coronal (f) FSE T1-weighted MR images obtained after addition of gadolinium showing the CM is surrounded by telangiectasia. In this case the telangiectasia is slightly visible also in an FSE T2-weighted sequence obtained without contrast injection. The effect of the hemosiderin is increased on the coronal T2-weighted sequence (e). The telangiectasia is evident on T1-weighted sequences after gadolinium administration. Venous caput medusae arises from the DVA and drains into the lateral recess (g).

**Fig. 4.** Case 4. Left: Follow-up MR image obtained at 12 months after initial presentation confirming the typical radiographic findings of the three vascular malformations. Right: Same examination, lower section, demonstrating enlarged venous radicles in the fourth ventricle.

**Fig. 5.** Case 5. Sagittal (left) and coronal (right) FSE T1-weighted MR images obtained after gadolinium administration revealing a CM surrounded by a capillary telangiectasia and DVA, with multiple drainages through the pons.
Neurovascular triad

The petrosal sinuses may have a major risk of hemorrhage related to a major pressure gradient. Developmental venous anomalies are part of the architecture of mixed vascular malformations, with varying neuroimaging evidence due to changeable hemodynamic phenomena. Developmental venous anomalies may be visible only after excision of the associated CM, supporting the suggestion that, besides local compression, some primary outflow impairment may cause a fugitive clouding of the DVA. Venous outflow restriction inside the DVA may trigger backward evolutionary changes in the dependent capillary–venous circulation. Stenosis or obstruction of the main venous collector with engorgement of the terminal radicles probably represents the main mechanism responsible for capillary hypertension, microhemorrhage, endothelial growth factor activation, and the origin of associated CMs. Among the cases presented here, we were able to demonstrate a stenosis of the main trunk only in the patient in Case 6 (Fig. 6). Coexistent dilation of the terminal radicles may indicate a hypertensive DVA (Fig. 7) with distal hemodynamic overload.

The Neurovascular Triad

The clinical profile of this triad is incompletely understood. Primary or late bleeding occurred in most of our cases at a specific location inside the pons and middle cerebellar peduncle, corresponding to the leaky cavernomatous chambers found in the surgical specimens (Fig. 2). In the only other report of this triad besides the present one, an incomplete panorama of the spectrum of this complex vascular malformation was described: the CM was nested in the radicles of the venous angioma and was independent of the telangiectasia. The neuroimaging profile of our cases demonstrated two basic relationships that had important surgical and pathogenetic implications: CMs within the telangiectasia and CMs related to the radicles of the DVA. The concomitant occurrence of these three vascular malformations secondary to somatic disruption of a gene (or genes) involved in angiogenesis and endothelial cell function in this specific brainstem area has been hypothesized.

Plummer et al. found that multiple mutations were needed to lead to the development of CMs; in their experimental study, a mixed vascular lesion composed of telangiectatic, venous, and cavernomatous elements developed when mice heterozygous for the KRIT1 mutation were crossed with mice homozygous for tumor suppressor p53 deletion. The unvarying pontine location of this complex malformation may also suggest that some local gene susceptibility factor may be triggered by flow-induced changes in the vascular endothelial cells at this anatomical site.

As a whole, histopathological findings in Cases 1 and 6 documented a mixed vascular malformation consisting of coalescent transitional venules and telangiectatic vessels (Fig. 2) fading into larger and loculated endothelial spaces that may represent immature cavernomatous chambers, a sort of missing link between telangiectasia and typical CMs. These discrete cavernomatous enclaves were not arranged as a separate entity, but were intermingled with telangiectatic and venous vessels, suggesting a continuum in the development and progression of this complex malformation. This finding may also provide early pathological evidence of that hemorrhagic angiogenic proliferation characterized by the formation, budding, and coalescence of new endothelial vascular spaces, indicating a de novo formation of a CM. Dilation and/or thrombosis inside a telangiectasia and in the radicles of a hypertensive venous malformation leading to compaction into a CM may also occur.

The correlation of pathological with MR imaging findings for CMs was clearly described by Zabramski et al. In particular, a Type I lesion is characterized by subacute hemorrhage surrounded by hemosiderin-stained gliotic brain tissue. The imaging findings of a presumed CM at the site of a hematoma do not always correspond to its full pathological evidence. The existence of a noncollagenized CM representing an immature form of the malformation has been recently suggested in an experimental model.

The underlying pathological features of hemorrhagic CMs within this complex vascular malformation may be more heterogeneous and less obvious than is believed. Our surgical specimens seem to demonstrate that hemorrhage occurred inside a hybrid pathological milieu corresponding in particular to loculated endothelial spaces and coalescent transitional capillary–venous vessels.

Treatment Options

In a mixed vascular malformation the CM constitutes the
actual surgical target, but it is difficult to recognize its boundaries where they fade into the telangiectasia. Besides the usual and obvious warnings regarding brainstem surgery, the surgical strategy depends on the mutual relationships occurring in this complex vascular environment, where the venous anomaly deeply interferes with the other malformations. Developmental venous anomalies with radicles in the floor of the fourth ventricle may hamper the approach to the underlying CM, and the usual entry zones may be disturbed by the overlying vascular tissue. Venous malformations were substantially preserved at surgery, but fine radicles were found in the surgical specimens, indicating intimate pathological blending in this subset. A CM embedded in a pontine telangiectasia (Case 2) represents a difficult surgical problem due to the continuous bleeding encountered during the approach to the CM through the telangiectatic neural tissue. Recent observations on recurrence of CMs associated with DVAs have demonstrated that new lesions had different pathological characteristics. The relevance of neuroimaging findings in the telangiectasia may be limited and extension of the lesion may go beyond that expected, as confirmed by correlations between MR imaging and pathological findings in telangiectatic areas that have no appreciable signal abnormalities. This occult telangiectatic milieu may be a reason for recurrence (in addition to residual CM) after excision of a brainstem CM, and should be carefully considered and investigated on preoperative MR imaging.

Conclusions

In this study we describe six patients with coexistent CMs, DVAs, and telangiectasia located in the pons. Overall, this vascular triad may represent a hypertensive system due to some venous restriction (congenital or acquired) of the pontine capillary–venous outflow. Hemorrhage, rebleeding, and growth of the associated CMs confirm the aggressive nature of these mixed lesions. The long-term follow-up findings demonstrate surprising evidence of evolutionary changes in the mutual relationships and ongoing progression of the component vascular lesions.

Acknowledgment

We acknowledge Dr. N. Acciarri for the artist’s drawing featured on the cover.

References

5. Barr RM, Dillon WP, Wilson CB: Slow-flow vascular malforma-
Neurovascular triad


Accepted May 18, 2007.

*Address correspondence to:* Eugenio Pozzati, M.D., Department of Neurosurgery, Bellaria Hospital, Bologna, Italy 40139. email: eugenio.pozzati@ausl.bo.it.