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Diagnostic Imaging

M. Forsting · I. Wanke (Eds.)

Intracranial Vascular Malformations and Aneurysms

From Diagnostic Work-Up to Endovascular Therapy

2nd Revised Edition

With Contributions by

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Foreword by

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With 189 Figures in 682 Separate Illustrations, 20 in Color and 9 Tables

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Foreword

Neuroradiology goes therapeutic.

By using the vascular system as an access route to intracranial vascular pathologies, many vascular diseases can be treated nowadays "from the inside" with only minimal invasiveness.

Neuroradiology has long ceased to be a purely diagnostic discipline. The need for a second edition of the book – edited, and to a significant degree written, by Prof. Forsting and Prof. Wanke – relatively soon after the first edition underlines the importance of and growing interest in Interventional Neuroradiology.

The editors focus on intracranial vascular malformations and aneurysms which, together, comprise a major proportion of the bread earned by the neurointerventionalist. The book not only deals excellently with interventional procedures, but also illuminates underlying pathological changes, different classification schemes, indications for endovascular therapy and relevant studies that have been conducted in this field.

Prof. Forsting and Prof. Wanke have been working in Interventional Neuroradiology for many years and have succeeded in recruiting a team of internationally renowned authors. Their volume on *Intracranial Vascular Malformations and Aneurysms* is not only of great interest to neuroradiologists, but also to colleagues working in the neighboring disciplines of Radiology, Neurology and Neurosurgery.

I am convinced that the second edition of *Intracranial Vascular Malformations and Aneurysms* will be at least as successful as the first one.

Göttingen — Michael Knauth

Preface

Four years after its first edition, we are happy to present the second edition of our book on diagnostic imaging and endovascular therapy of vascular malformations.

The need for a second edition within a relatively short period of time indicates that interventional neuroradiology and knowledge about vascular malformations is still a fast growing field. It is a 2nd edition with new images and major text changes, as well as the corresponding literature update. Also new about the book is that it now has two editors. Isabel Wanke and myself hope that this new edition will be as successful as the first and that it will also help many colleagues to improve their knowledge of non-atherosclerotic vascular problems of the brain.

Essen

Michael Forsting
Isabel Wanke

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Developmental Venous Anomalies

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Michael Forsting and Isabel Wanke

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KEY POINTS

- Developmental venous anomalies (DVAs) represent the most common vascular variant
- DVAs consist typical of medullary veins forming a caput medusae draining into a transcerebral collector vein which empties into a dural, subependymal or cortical vein
- DVAs are low-flow, low-resistance abnormalities draining normal brain parenchyma!
- DVAs have been associated with vague neurological symptoms, such as nonspecific headaches and dizziness, or with seizures. In most cases it is an incidental finding
- Up to one third of DVAs is associated with cavernomas; therefore susceptibility weighted MRI-sequences should be included into the imaging protocol, especially if a seizure was the indication for the examination. Therapy should be focussed on the cavernoma
- Rarely, congenital abnormalities (e.g. heterotopia) might also be associated with DVAs
- Venous thrombosis in DVAs might occur but no more often than in any other intracranial vein
- Surgical resection or radiation therapy of DVAs should be avoided
- Endovascular therapy of DVAs is also not an option

In a typical neurovascular working day, developmental venous anomalies (DVAs) cause a lot of confusion. In part, this confusion is related to the term "venous angioma", which is used in many institutions as a synonym for DVAs! But "venous angioma" is clearly a misnomer, because the term "angioma" usually suggests a severe disease with a substantial risk of bleeding. In contrast, DVAs must be considered as unusual, but nonpathological, venous drainage and an embryological determined variant of venous drainage. On the other hand, DVAs are considered to be the most common form of cerebral vascular malformations, occurring in up to 4% of the population (Garner et al. 1991; Ostertun and Solymosi 1993; Truwit 1992). This high incidence is a good reason to familiarize oneself with these lesions and keep abreast of new findings in this area.

Another factor contributing to the DVA-related confusion is that many radiologists and clinicians just see abnormal vessels on magnetic resonance imaging (MRI) scans, immediately tell the patient something about a vascular malformation, and refer the patient for neurosurgical extirpation of the lesion.

To avoid too much irritation, specifically within the group of referring doctors, the term "venous angioma" should be avoided and DVA should be used. However, if you are reporting about DVA, it is usually necessary to explain what this is. And this is a good reason to read the upcoming chapter.

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1.1 Pathology

The pathogenesis of a DVA is still unknown. Saito and Kobayashi et al. (1981) hypothesized that an intrauterine event during formation of the medullary veins or tributaries induces the formation of the collateral venous drainage pathways. This hypothesis is supported by the absence of normal draining veins in the region of the large draining collector vein.

Another assumption is that an in-utero acquired venous occlusion maintains the intrinsic venous anastomoses within the white matter. The DVA then expresses an early collateral adaptation, but develops on a pre-existing venous system that has been transformed. However, the majority of DVAs are not associated with any sort of neural tissue damage or dysfunction. Lasjaunias (1997) commented on this theory to the effect that it can hardly be imagined that a significant venous disorder (such as thrombosis) at an early stage of development would not be associated with some tissue abnormality. Furthermore, the fact that DVAs do not exist in the diencephalons, brain stem, or spinal cord and are only encountered where tectum derivates exist, excludes DVAs from the group of pathological malformations (Lasjaunias 1997).

The association of venous malformations with other vascular malformations gave further room for speculation. Mullan et al. (1996) hypothesized that true arteriovenous (AV) malformations may be fistulized venous malformations and that both vascular anomalies may be related to a developmental failure of the cortical venous system. However, these are nice theories, but do not have any impact on diagnostic work-up or patient management, nor are they supported by any study. Kilic et al. (2000) looked for expression of structural proteins and angiogenic factors in cerebrovascular anomalies. Whereas AVM and cavernomas had expression of vascular endothelial growth factor, DVAs did not express any of the studied growth factors and mainly consisted of structural proteins of angiogenically mature tissue. This finding strongly supports the idea of a simple variation of the venous drainage instead of being a true vascular malformation.

In contrast, the relationship of DVAs with cavernous hemangiomas has been well documented (Abe et al. 1990; Comey at al. 1997; Goulao et al. 1990; Rigamonti and Spetzler 1988; Wilms et al. 1994). There are also reports about de novo formation of cavernous hemangiomas in the vicinity of DVAs (Ciricillo et al. 1994; Campeau and Lane 2005). The close relationship of mixed malformations may be related to venous hypertension within the regional microenvironment with erythrocyte diapedesis and angiogenic growth factor release (Cirillo et al. 1994; Robinson et al. 1995). Another interesting finding is that in families affected with cavernomas – an autosomal dominant inheritance has been established in these families – none of the patients described to date with the combination of cavernoma and DVA has a positive familiar history, nor has any genotypic classification been found. However, we have to accept the coincidence between DVA and cavernomas, but have to admit that we do not have any substantial hypothesis as to what the pathogenetic origin of this coincidence is.

The histologic examination does not reveal any vessel abnormality. The vessel wall is completely normal in DVAs. The abnormality in DVAs is the course of the draining vein (Figs. 1.1–1.3). There is no arterial component in this entity. Intervening brain tissue is present between the veins compromising the lesion, and this brain tissue is usually of normal signal without evidence of hemosiderin staining or gliosis. On MRI there is sometimes a high T2-signal between visible around the draining vein. However, this should not be interpreted as gliosis, but can be explained by dilated perivascular and cerebrospinal fluid (CSF)-containing space (Fig. 1.4). In up to 30%, locoregional brain atrophy could be detected adjacent to the DVA (San Millán Ruíz et al. 2007).

Developmental venous anomalies represent the most common vascular variant, accounting for 63% of intracranial vascular malformations in one large autopsy study, with an overall incidence of 2%–4% (Sarwa and McCormick 1978). The lesion consists of a tuft of abnormal enlarged medullary venous channels that are radially arranged, and drain into a central venous trunk. The common trunk drains intracerebrally into the deep of superficial venous system (Lasjaunias 1997). It is important to bear in mind that the vein's course is not normal; however, it does drain normal functioning brain tissue. This should be of particular interest when surgery has to be performed around the draining vein, e.g. if the DVA is associated with a cavernoma. In these patients it is of the utmost importance to preserve the draining vein and to remove the cavernoma (Fig. 1.5).

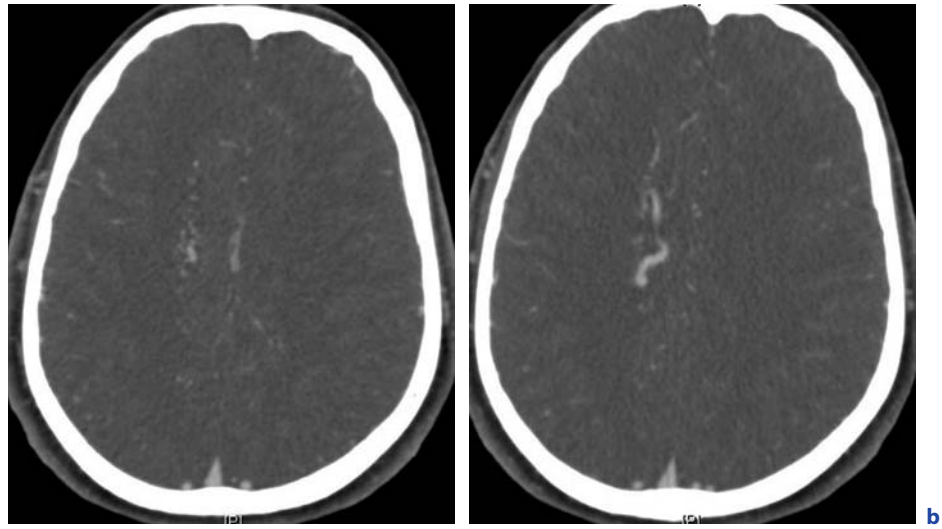


Fig. 1.1a,b. Contrast-enhanced CT shows the typical appearance of a developmental venous anomaly with medullary veins (**a**) draining into a collector vein with a transcerebral course (**b**)

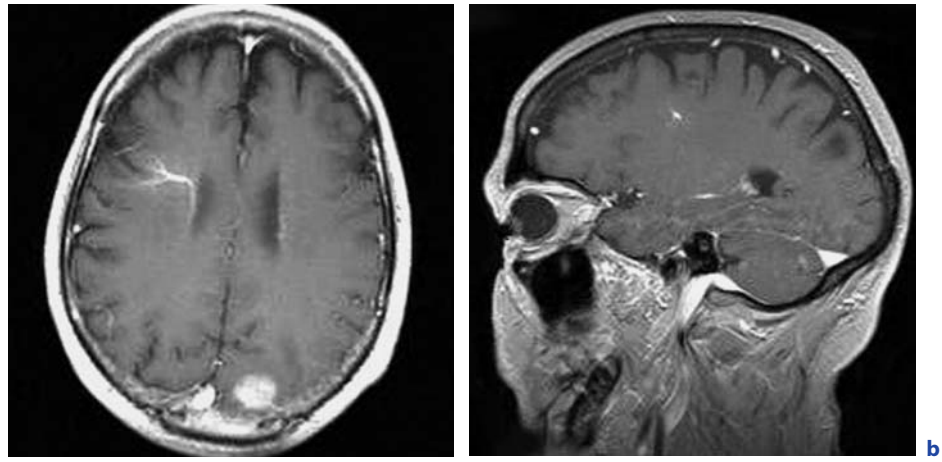


Fig. 1.2a,b. Axial (**a**) and sagittal (**b**) contrast-enhanced T1-weighted magnetic resonance imaging with a typical right frontal developmental venous anomaly. Conspicuous on both views is the transcerebral draining vein. A second look reveals the "Medusa head", small venules radially arranged around and draining into the transcerebral collector vein

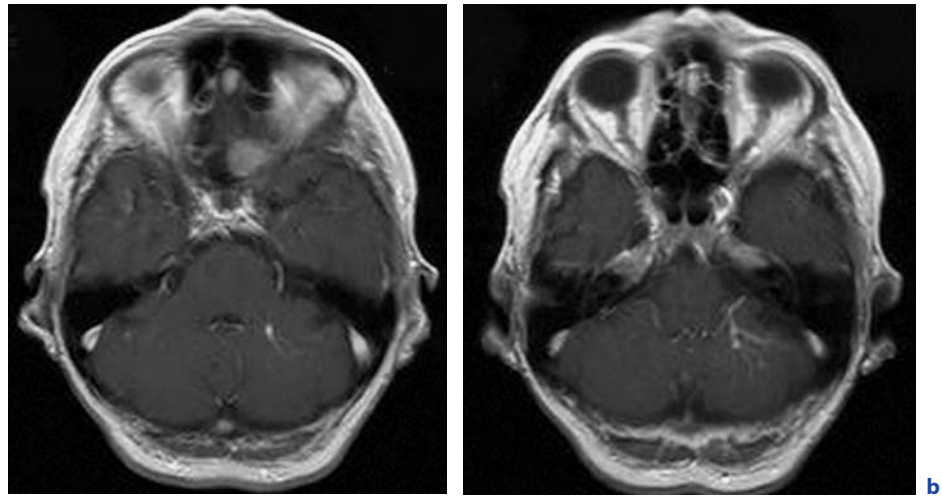


Fig. 1.3a,b. Axial contrast-enhanced T1-weighted magnetic resonance imaging with a developmental venous anomaly located in the left cerebellar hemisphere. Again, the transparenchymal draining vein is the most striking sign. In (**b**), the Medusa head is clearly visible. There is no need for an additional digital subtraction angiography

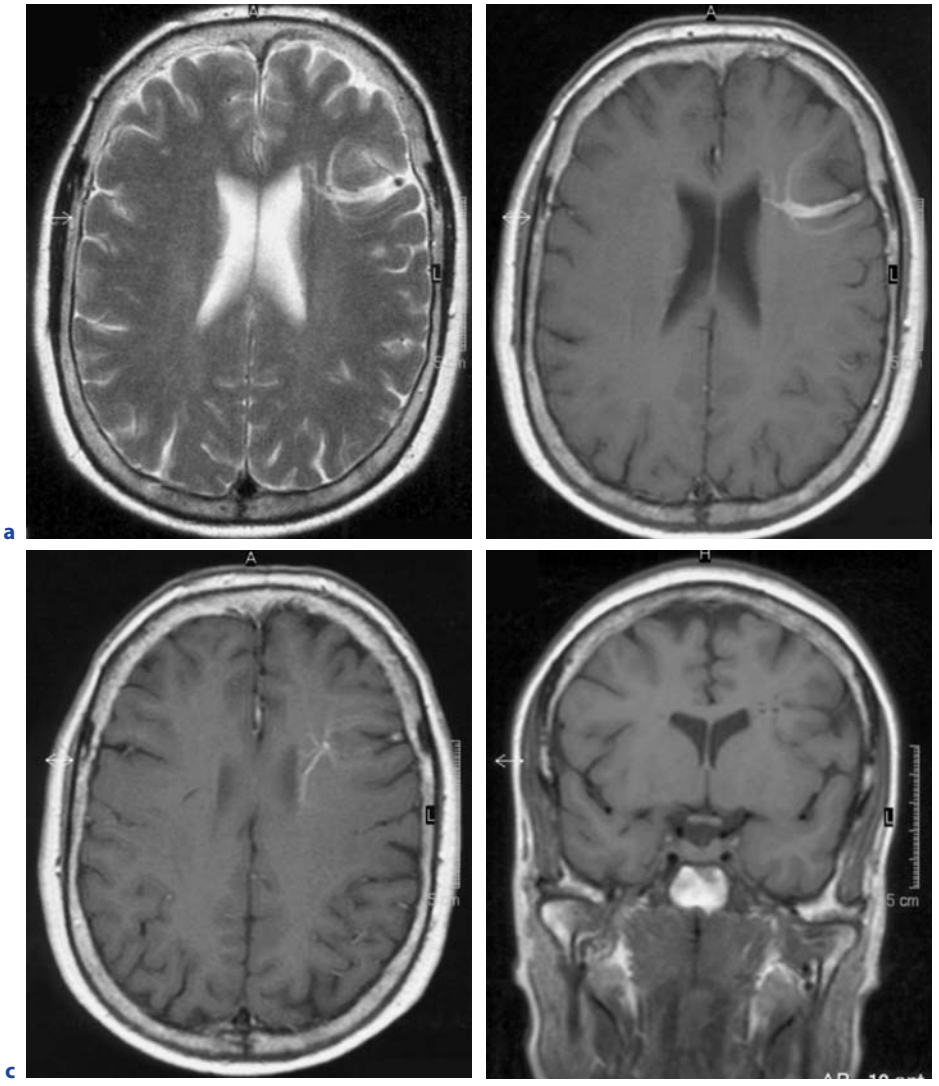


Fig. 1.4a–d. Axial T2-weighted (**a**) and contrast-enhanced T1-weighted (**b**) magnetic resonance imaging reveal a large transcerebral draining vein. Note the enlarged perivascular space around the vein on T2 image (**a**) and the coronal T1 image without contrast enhancement (**d**). The Medusa head is visible with star-like configured small draining venoles (**c**)

1.2 Clinical Presentation

Hemodynamically, DVAs represent low-flow, low-resistance lesions that are less likely to bleed. Garner et al. (1991) calculated the hemorrhage rate to be 0.22% per year; McLaughlin et al. (1998) found a symptomatic hemorrhage rate of 0.34% per year. This range of hemorrhage risk is within the range we expect from cavernous hemangiomas alone. Based on these data and on hemodynamics, one might already conclude that hemorrhages in the presence of a DVA are not related to the DVA itself, but in nearly all patients related to an associated cavernous angioma! Our opinion is that the risk of hemorrhage in a pure DVA is around zero! There exists not a single case report with a well documented intracerebral hemorrhage (ICH) due to a pure DVA. However, this is not evidence-based, just a simple clinical impression gained over the years. In all cases mentioning a pure DVA as the cause of an ICH, imaging was not optimal and did not rule out the more common constellation with an associated cavernoma.

The coincidence of DVAs and cavernomas, however, is evidence-based and therefore has to be taken into consideration whenever facing a cavernoma or a DVA. Up to one third of DVAs are associated with cavernomas (Figs. 1.5–1.9).

A major problem of most studies reporting hemorrhages due to a DVA is how they ruled out an associated cavernoma. It is clearly not enough just to obtain T2-weighted images in patients with DVAs. All

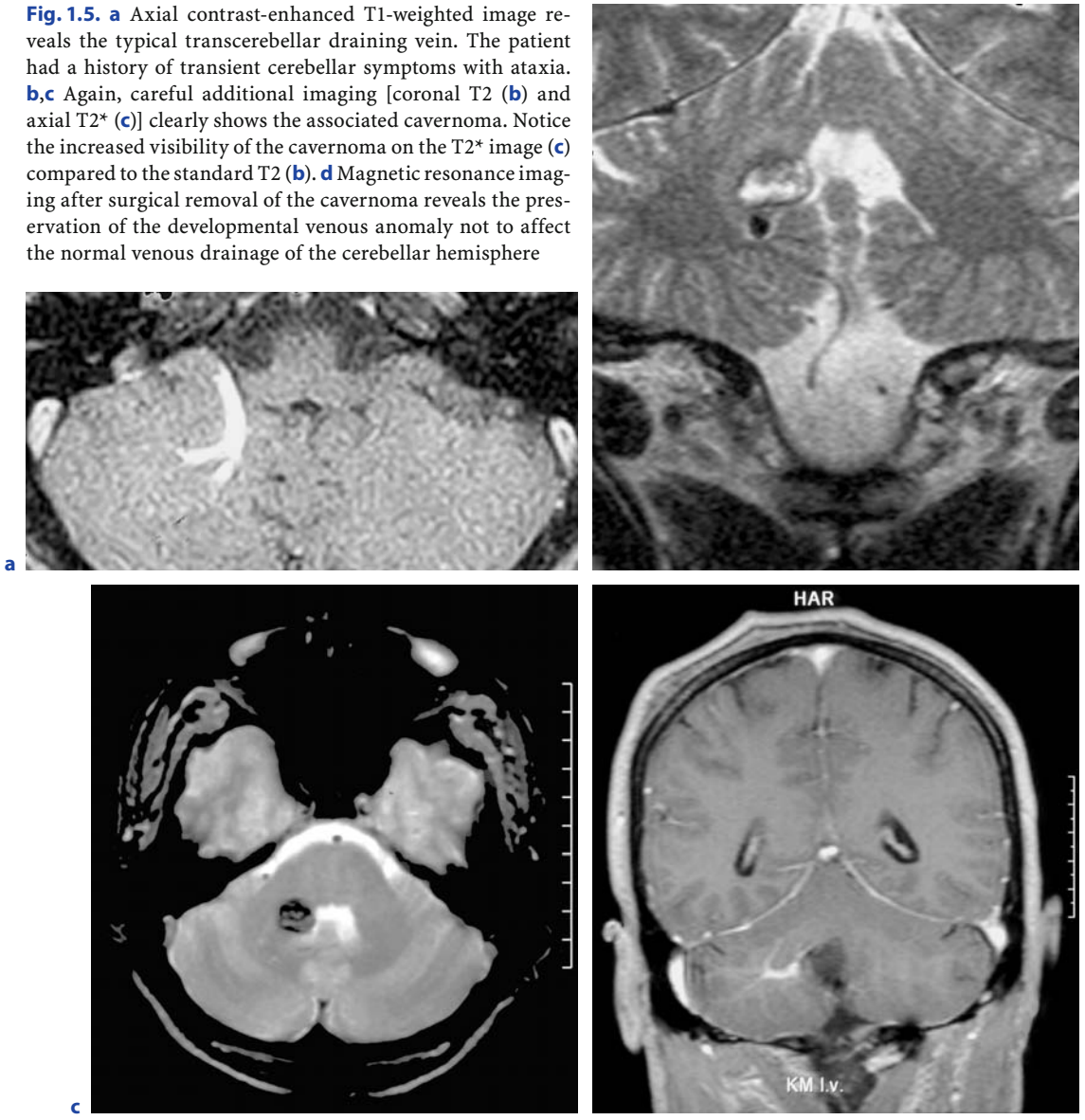


Fig. 1.5. a Axial contrast-enhanced T1-weighted image reveals the typical transcerebellar draining vein. The patient had a history of transient cerebellar symptoms with ataxia. **b**,**c** Again, careful additional imaging [coronal T2 (**b**) and axial T2* (**c**)] clearly shows the associated cavernoma. Notice the increased visibility of the cavernoma on the T2* image (**c**) compared to the standard T2 (**b**). **d** Magnetic resonance imaging after surgical removal of the cavernoma reveals the preservation of the developmental venous anomaly not to affect the normal venous drainage of the cerebellar hemisphere

these patients need an imaging work-up with T2*-weighted MRI sequences to exclude or to visualize associated cavernomas with the highest sensitivity.

Beside the risk and discussion of hemorrhagic complications, DVAs have been associated with vague neurological symptoms, such as nonspecific headaches and dizziness, or with more specific symptoms and/or signs like seizures (McLaughlin et al. 1998).

However, having in mind the association of cavernoma and DVA, all these findings have to be critically reviewed. In 1998, McLaughlin and colleagues published their series on 80 patients with DVAs focused on the prospective natural history of cerebral developmental venous malformations. According to their interpretation, 22/80 DVAs were symptomatic: 9 patients had headaches related to the DVA, 4 presented with DVA-related seizures. Three patients had sensory symptoms, three other patients motor deficits. Two patients presented with trigeminal neuralgia and a single patient with an extrapyramidal movement disorder. Korinth et al. (2002) described another patient with trigeminal neuralgia due to a DVA in the cerebellopontine angle. After microvascular decompression, the typical symptoms of the neuralgia disappeared completely. At the time of

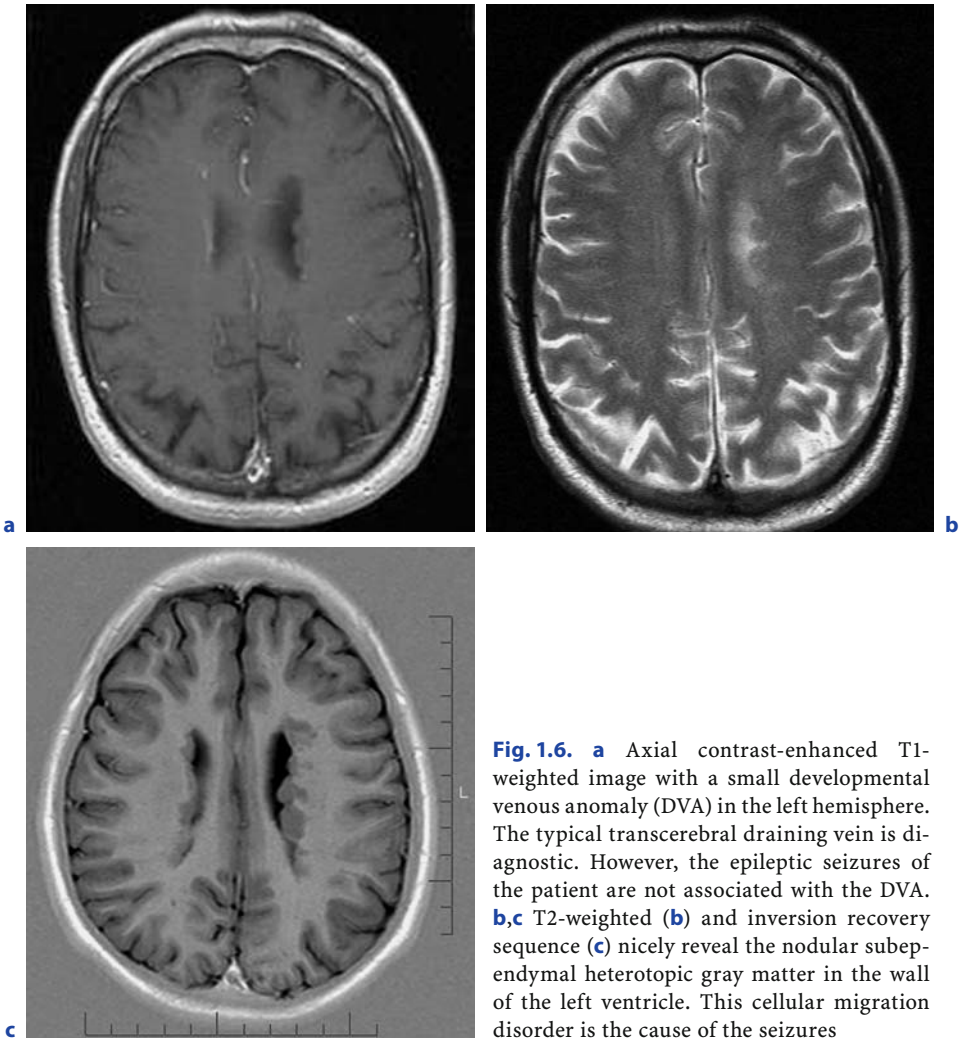


Fig. 1.6. **a** Axial contrast-enhanced T1-weighted image with a small developmental venous anomaly (DVA) in the left hemisphere. The typical transcerebral draining vein is diagnostic. However, the epileptic seizures of the patient are not associated with the DVA. **b**,**c** T2-weighted (**b**) and inversion recovery sequence (**c**) nicely reveal the nodular subependymal heterotopic gray matter in the wall of the left ventricle. This cellular migration disorder is the cause of the seizures

registration, 16/18 patients in the McLaughlin series had sustained previous intracranial hemorrhage in the region of the venous malformation and 2 of them suffered subsequent hemorrhage during the prospective follow-up period. Most of the venous malformations were located in the posterior fossa (36/80). In 3 patients, there was an association of the DVA with a cavernous hemangioma. McLaughlin and colleagues did excellent work while collecting one of the most important papers dealing with DVAs.

However, it is questionable whether the symptoms of the patients were really related to the DVA. It is not surprising that a substantial proportion of patients with these lesions reaching neurosurgical centers had some history of associated neurological events. Such selection is not unusual and is likely to overestimate the risk of any associated neurological manifestation. Symptoms like headache and sensory symptoms are difficult to dissociate from the lesion, but it is also often impossible to attribute the symptoms causally to the DVA. Another problem of the study is that imaging was not optimized to get maximal sensitivity for cavernomas. Symptoms like bleeding, seizures, and headache are known to be associated with cavernomas. Therefore, T2*-weighted MRI sequences should be standard for all DVA imaging protocols. However, some patients really might have local symptoms due to the large calibre of the DVA in the cerebellopontine angle. Abdulrauf et al. (1999) found a coincidence of cavernous malformation and DVA in 24% of patients referred for surgical removal of a cavernous malformation. They additionally deduced that, specifically in the posterior fossa, the likelihood of an association of both entities increases significantly. Another interesting hypothesis of them is that association of a cavernoma and a DVA may increase the probability

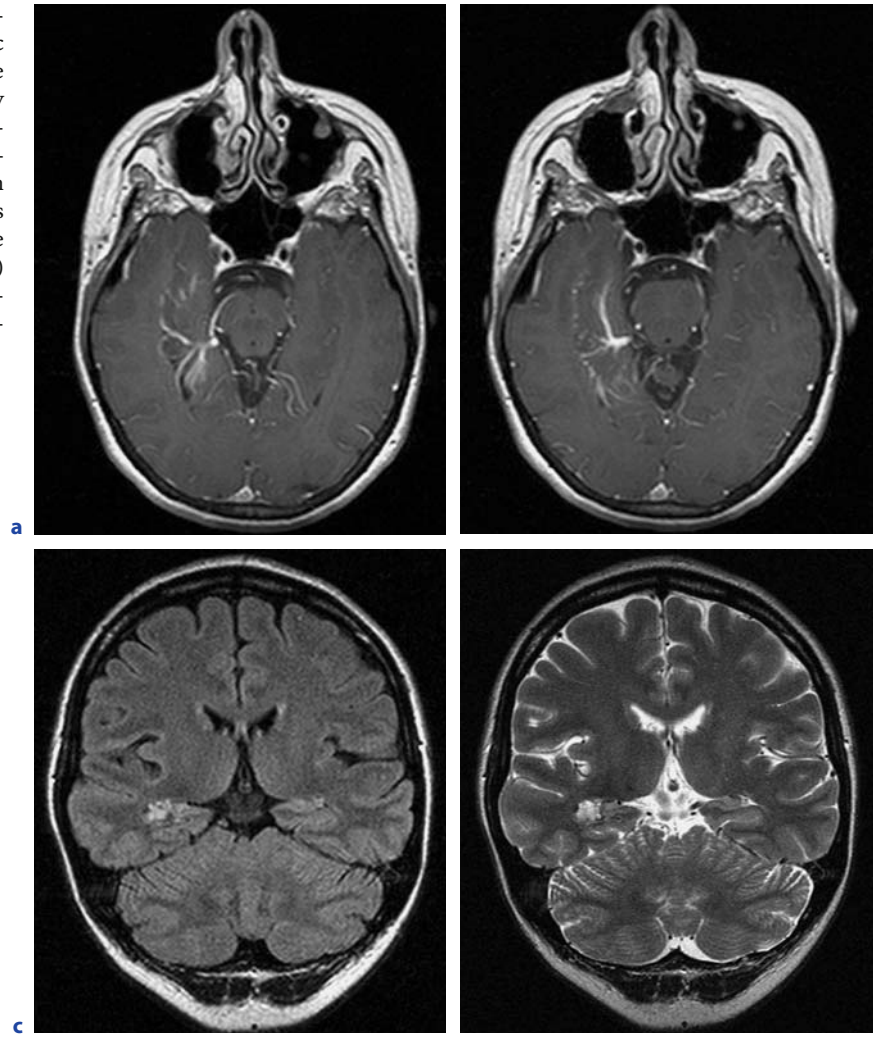


Fig. 1.7. a,b Axial contrast-enhanced T1-weighted magnetic resonance imaging with a large developmental venous anomaly (DVA) located in the right temporal lobe. The patient was referred with the diagnosis of an arteriovenous malformation as causative for his temporal lobe epilepsy. **c,d** Coronal FLAIR (**c**) and T2-weighted (**d**) images revealed a typical cavernoma associated with the DVA

of a cavernoma-related hemorrhage. In their study population, 38% of patients with cavernoma alone presented with hemorrhage, but 62% of patients with cavernoma and DVA. Additionally, the incidence of repeated symptomatic hemorrhage was increased in the group with combined malformations (23%) compared to the pure cavernoma patients (9.5%). Comey et al. (1997) described similar cases with parenchymal enhancement around the DVA, and speculated that this finding might be secondary to local venous hypertension. Other surgeons (Little et al. 1990) found an anatomical and physiological communication between cavernomas and associated DVAs. Therefore, it might indeed be possible that venous hypertension in association with DVA can predispose a cavernoma to bleed. Another explanation for this finding may be that the majority of cavernomas were located in the supratentorial compartment, but the majority of cavernomas plus DVA were located in the infratentorial compartment. Because of their eloquent location, it is likely that smaller hemorrhages in the posterior fossa manifest overt symptoms and may hence be detected clinically.

Töpper et al. (1999) reported 67 patients with the MRI-based diagnosis of DVA. In 12 patients, an associated cavernoma was found. And again: there was no hemorrhage in a patient with a pure DVA. All hemorrhages were due to an associated cavernoma.

The first thing to remember in clinical presentation of DVA is that there is no or at least an extremely low risk of hemorrhage due to a DVA. All hemorrhages are probably related to an associated cavernoma. You just have to find the cavernoma or urge a radiologist to do so. In acute hemorrhage it could be difficult to define a cavernoma on CT or MRI as a source for the bleeding since calcifications might be invisible on CT

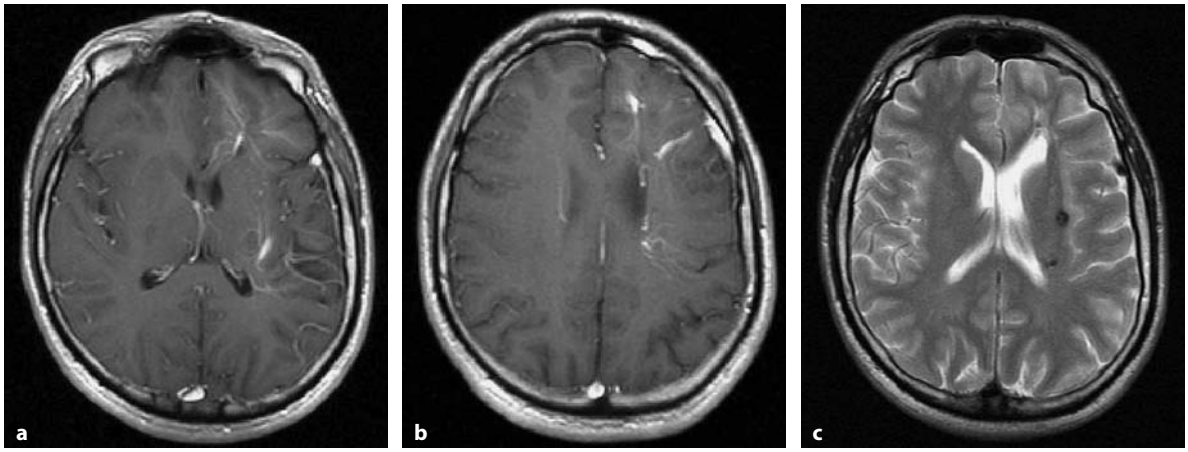


Fig. 1.8. a,**b** Patient with two interconnected developmental venous anomalies (DVAs) periinsular and frontal on the left side (contrast-enhanced T1-images). **c** T2-image reveals additional intracerebral cavernomas

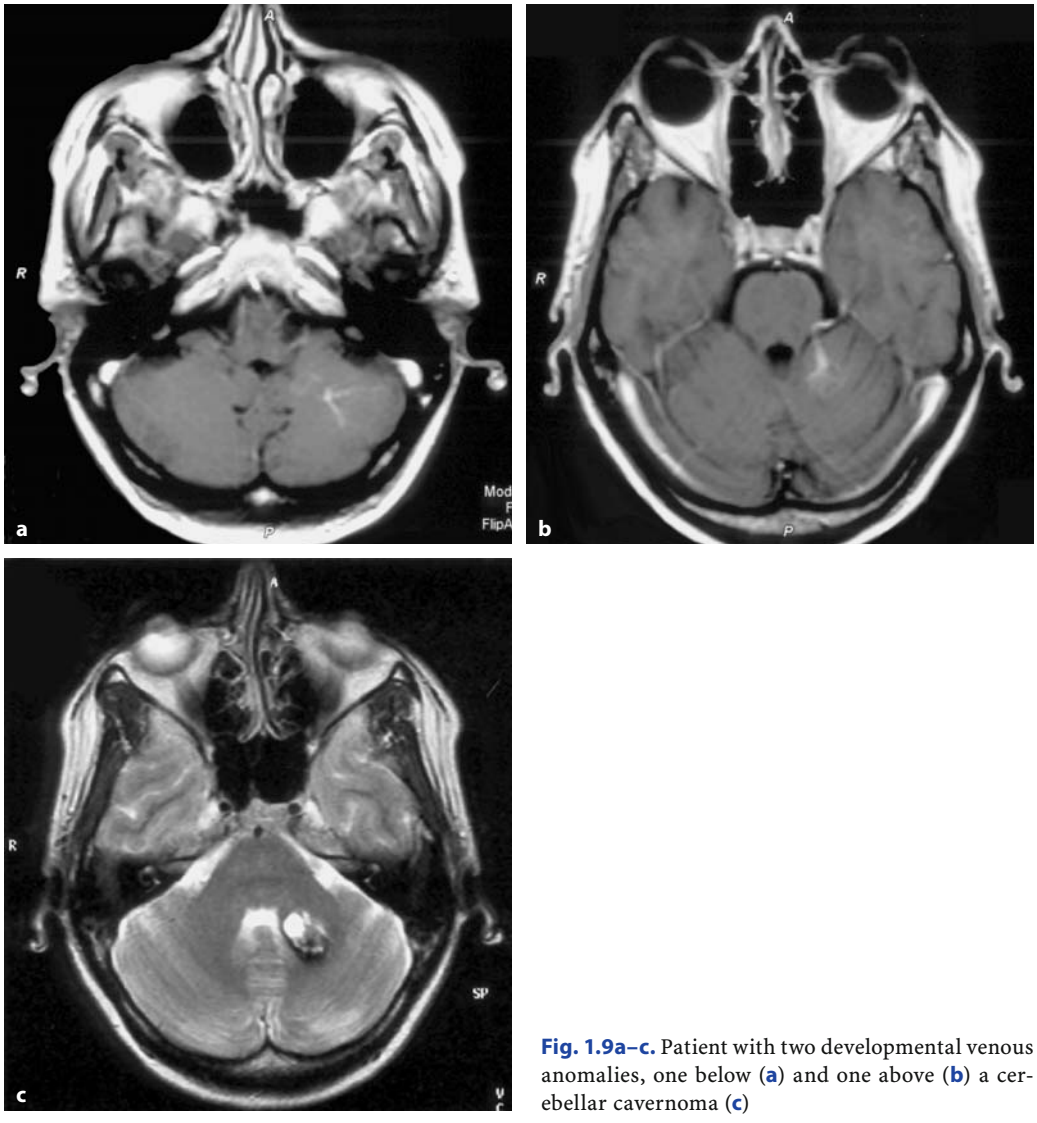


Fig. 1.9a–c. Patient with two developmental venous anomalies, one below (**a**) and one above (**b**) a cerebellar cavernoma (**c**)

and the popcorn like shape is not as obvious on MRI in the acute phase. But in association with a DVA a cavernoma should be considered (Fig. 1.10a–g).

In Töpper's study, the main reason for referring the patient to the MRI suite included seizures and headaches. In contrast to McLaughlin, these authors did not find any association between the complaints that led to MRI and the location or diagnosis of a DVA. In both groups there were a lot of patients with headaches and epilepsy; in fact, these two groups represent the main referral reason in both groups. Whereas McLaughlin classified many DVAs as symptomatic, because the patients suffered from headaches, Töpper and colleagues never found an association between headache and a DVA. And we agree: we do not think that there is an association between DVA and headache. Remember, DVAs do not cause any steal effect (like true AVMs), and it is more than difficult to explain how the pathomechanism for headache could be. In general, there are two explanations for the coincidence of headaches and DVAs in the same patient. First, both findings are common and there is no causal relationship at all. Second, a small subgroup of patients with DVA and headache might have an additional cavernoma located near the surface of the brain. Some of these patients suffer from headache due to subarachnoid microhemorrhages. And then again, the cavernoma is responsible for the clinical picture and not the DVA.

Another reason for patient's referral to a MRI unit is seizures (Gümüs et al. 2007). There might be an association between DVA and epilepsy, even if the EEG focus is not congruent with the location of the DVA. If this is true, one should take a careful look for an associated cavernoma, cavernomas being known to cause different types of epilepsy, mainly due to their content of hemosiderin.

And if you do not find a cavernoma as a source for the ictus, there is little evidence that the development of a DVA during embryology might be associated with some more severe developmental problems like small-scale deficits (Barkovich 1988; Watanabe et al. 1990). Lasjaunias (1997) pointed out that the DVA is clearly not responsible for the cortical changes. However, the coincidence of both findings illustrates the close relation in topography and time between the venous maturation process (from the striatal veins and transhemispheric balance setup) and the cell migration from the germinal matrix.

In conclusion, seizures and DVAs are a complex combination (see Figs. 1.6 and 1.7). It is clearly incorrect and too simple to decline any association between the clinical problem and the imaging findings on the one hand, or to identify the DVA as the epileptogenic foci in all patients on the other. However, any DVA in a patient with seizures should guide us to look careful for cavernomas (associated with the DVA or at any other location within the brain) or any neuromigrational anomalies (e.g. polymicrogyria, heterotopia) (Riel-Romero and Mattingly 2005).

There was another interesting topic in the study of Töpper et al. (1999). Among those patients referred to a private practice group, the incidence of DVA was 0.14%; among those referred to a university department of neuroradiology, the incidence was 0.7%. The authors figured out that this difference can be explained by the different numbers of patients who undergo a contrast-enhanced MRI in a private practice compared to a university department. Contrast-enhanced MRI studies increase the sensitivity of MRI for DVA significantly.

To come back to the discussion of hemorrhage in patients with DVA, a rare reason for hemorrhage around the collecting vein in DVA may be a thrombosis of the draining vein (Bouchacourt et al. 1986; Masson et al. 2000). There are only a few case reports in the literature about this specific problem and there is no evidence that the risk of venous occlusion is increased in DVA. Thrombosis of the collector vein might occur also without hemorrhage and cause venous infarction (Konan et al. 1999). But, of course, the transcerebral draining vein might have a risk of thrombosis like all other intracranial veins. It seems to be true that thrombosis of the main draining vein does cause more severe clinical problems if located in the posterior fossa. Bouchacourt et al. (1986) reported a well-documented case of thrombosis of a DVA that led to an extensive hemispheric venous infarction. Usually, the outcome is pretty good, with and without anticoagulation. Rarely, DVAs have been reported to cause hydrocephalus or trigeminal neuralgia (Blackmore and Mamourian 1996; Numaguchi et al. 1982; Yagmurlu et al. 2005) due to local compression of the aqueduct or the fifth cranial nerve. There is a single case report describing the juxtaposition of capillary telangiectasia, cavernous malformation, and DVA in the brainstem (Clatterbuck et al. 2001). The authors' hypothesis is that a developmental event may disrupt local capillary-venous pattern formation.

Jung et al. (1997) described a patient with a DVA and an acute demyelination around the draining vein. However, there is no evidence that DVA may

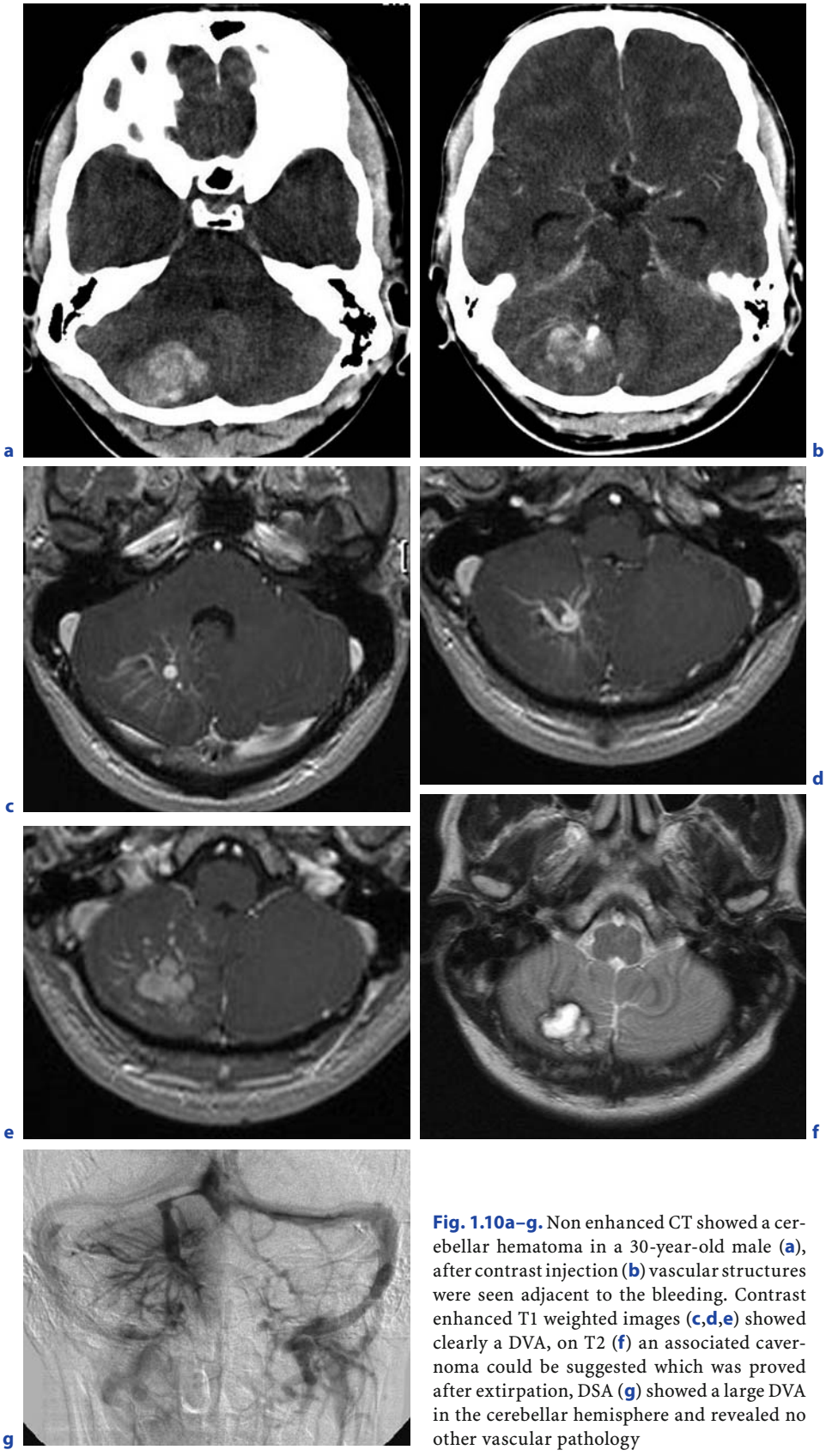


Fig. 1.10a–g. Non enhanced CT showed a cerebellar hematoma in a 30-year-old male (**a**), after contrast injection (**b**) vascular structures were seen adjacent to the bleeding. Contrast enhanced T1 weighted images (**c**,**d**,**e**) showed clearly a DVA, on T2 (**f**) an associated cavernoma could be suggested which was proved after extirpation, DSA (**g**) showed a large DVA in the cerebellar hemisphere and revealed no other vascular pathology

lead to any other central nervous system (CNS) disease and cases like this merely represent an occasional coincidence.

Under rare circumstances, DVA can also be associated with tumoral masses (Beers et al. 1984; Handa et al. 1984). Handa et al. (1984) reported a patient with a deep DVA combined with an intracranial varix.

Most of the DVAs are solitary, although multiple lesions might occur in the blue rubber bleb naevus syndrome, characterized by bluish discolored skin and mucocutaneous lesions. However, there are multiple DVAs in patients that do not have any syndromes or any genetic defect (Figs. 1.8 and 1.9), but the likelihood of a coincident cavernoma seems to be increased in these patients.

1.3 Imaging

Computed tomography (CT), MRI, and angiography delineate the typical curvilinear vascular channels receiving drainage from a "Medusa head" – the typical radial pattern of small venules. The larger, central draining "collector" vein empties into a large cortical, a dural, or a subependymal vein.

The typical contrast-enhanced CT or MRI reveals the draining vein as an enhancing "dot" within the white matter of the supratentorial hemispheres or the cerebellar hemispheres.

Going up or down slice by slice, this enhancing dot is visible within a couple of slices. It depends mainly on slice thickness and on contrast resolution whether the Medusa head is visible or not. Due to the improved contrast resolution, the draining vein is usually better delineated on MRI than on CT. DVAs may be overlooked on unenhanced MRI scans, but usually the large central vein can be seen due to its linear flow void. Sometimes the draining vein has a high signal on Tl-weighted images due to slow flow rephasing phenomena. This is important to know, because otherwise some radiologists and/or clinicians misinterpret this high signal as a sign of thrombosis! There is nearly always some CSF signal around the vein. As mentioned above, this should not be interpreted as a gliotic reaction of the brain, but simply as dilated perivascular spaces.

Intravenous contrast application usually visualizes not only the draining vein, but also the Medusa head to an extent where the diagnosis can be confirmed by MRI or CT. Angiography is usually unnecessary.

However, finding a DVA on MRI should always initiate a modification of the scanning protocol. This is particularly important in those patients referred because of seizures. As mentioned above, DVA can be associated with other cortical abnormalities. The theory of increased cortical disorders came up with the hypothesis that DVA might have a pathogenetic origin in a specific intrauterine phase with occlusion of one of the major venous sinus. To obtain venous drainage, one of the transmedullary draining veins is kept open, and during this vulnerable phase, other developmental problems might occur that finally cause seizures. In conclusion, if you do not find a cavernoma in seizure patients, look for heterotopia, best visualized with inversion recovery sequences.

In the majority of patients with DVA and seizures, we have to look for associated cavernomas. This association is evident; however, nobody really knows the pathogenetic background behind it. But it is also evident that we do not see all cavernomas on regular T2-weighted images, e.g., not the small ones. Therefore, in all patients with DVA (and specifically in those with seizures), a T2* gradient echo sequence has to be added to the usual protocol to be sure that there is no associated cavernoma. It is pretty sure that, in the majority of patients published in the literature as having an epileptic focus in the proximity of the visible DVA (and consequently the DVA was thought to be responsible for the seizures), the diagnostic work-up was not specifically designed to rule out a cavernoma with sufficient sensitivity. Additionally, T2* sequences sometimes visualize the DVA itself pretty well with a marked hypointensity reflecting the paramagnetic deoxyhemoglobin within the venous blood. Maybe MRI at 7T may facilitate diagnosis and comprehension of the underlying pathophysiology. First experience using 7T is promising in delineating this abnormality (Figs. 1.11 and 1.12).

There is still a debate about the usefulness of MRA in DVA. The transcerebral vein is usually visible, but MRA is clearly not necessary to confirm the diagnosis. To sum up the imaging findings, DVA is most often an incidental finding on cross-sectional imaging. On FLAIR or T2 weighted sequences the abnormality is sometimes seen as very vague, on CISS sequences it presents as isointense to venous sinuses, and diagnosis is much facilitated after contrast injection (Figs. 1.13 and 1.14). If the patient is

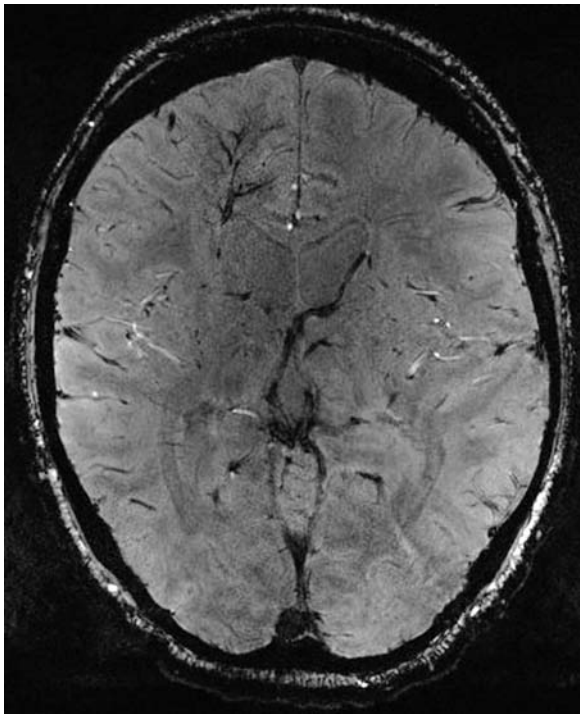


Fig. 1.11. Right frontal DVA on SWI sequence at 7 Tesla

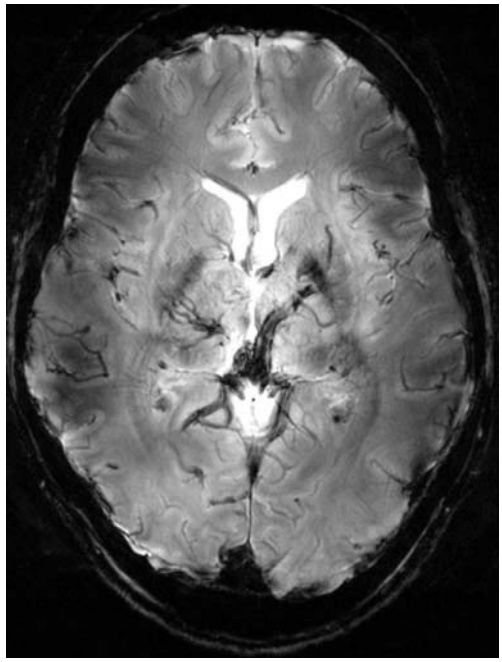
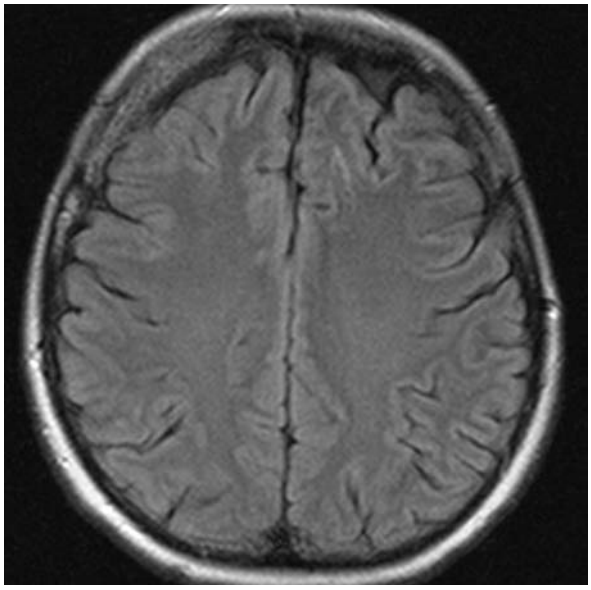
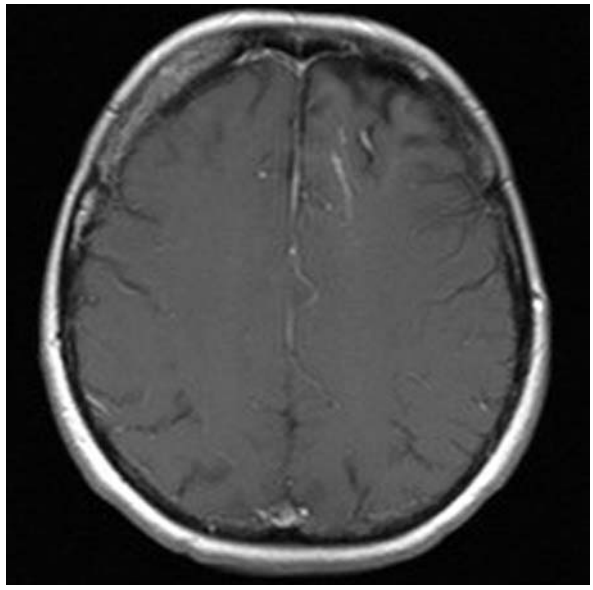


Fig. 1.12. Bithalamic DVA on gradient echo sequence at 7 Tesla; note the obvious delineation of the medullary vessels

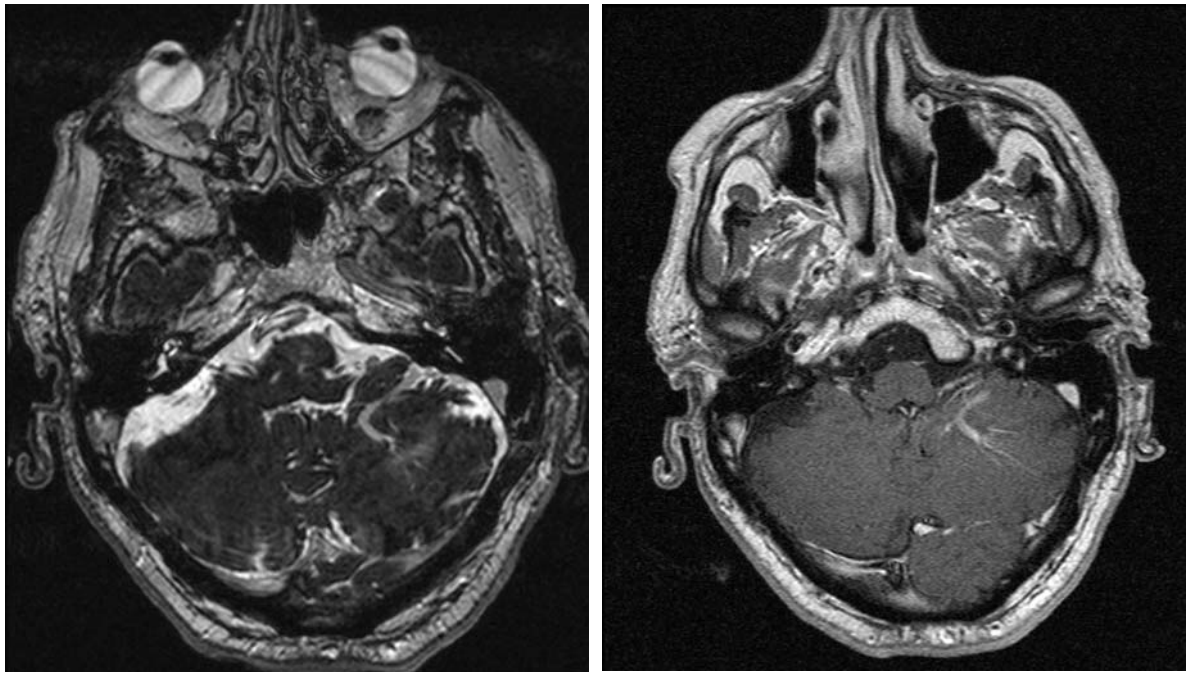


a



b

Fig. 1.13a,b. FLAIR sequence (**a**) with a faint tubular signal abnormality left frontal; on T1 with contrast (**b**) a DVA was clearly diagnosed



a b

Fig. 1.14a,b. Patient examined for tinnitus. CISS sequence showed tubular structure with the same signal intensity as the sigmoid sinus. Again, after contrast injection diagnosis of a DVA is obvious

referred for symptoms like seizures or headache, the imaging protocol should include a T2*-weighted sequence to exclude an associated cavernoma.

In a nonenhanced CT scan, the transcerebral draining vein can rarely be seen as a slight hyperdense dot or band within the white matter. In enhanced scans or in source images of CT angiography (Fig. 1.1), the vein is clearly visible – like in contrast-enhanced MRI (Peebles and Vieco 1997) (Fig. 1.15). However, if the diagnosis is based on typical MRI findings, it is not necessary to perform an additional CT scan or a CT angiography.

Angiographic characteristics include normal arterial and capillary phases, with opacification of the DVA exclusively during the venous phase which remain opacified through the late venous phase. The only abnormal finding is the Medusa head and the abnormal transcerebral course of the collecting vein (Figs. 1.10g and 1.16).

In general, we do not need angiography in patients with DVA. At our institution, we do perform angiography in those cases with an "atypical appearance" of the DVA, previous hemorrhage, or in the setting of hereditary hemorrhagic telangiectasia (with a high prevalence of true AV malformations, as well as venous anomalies).

Discussing the need for angiography in DVA, there is always somebody around putting the question of whether or not to rule out an AVM. This question clearly is not an indication for angiography in the vast majority of patients. Reports in the literature on the coincidence of DVA and true AV malformations are rare. Komiyama et al. (1999) figured out that there are 31 patients in the literature that had a DVA with an arteriovenous shunt. They themselves saw three patients, but they did not publish any MR images.

And if you read the reports carefully and look at the illustrations, you hardly ever find a typical DVA illustration on a cross sectional image. They are always atypical: large venous convolutes not just a single transcerebral vein and often already dilated arteries. So, the general recommendation to perform a DSA in those DVAs that have an atypical presentation on MRI can be justified (Seiz et al. 2007); this will lead to some AVMs that on a quick view look like a DVA on cross-sectional imaging. The chance, however, of missing an AVM in a patient with a typical DVA on MRI is really low and probably much lower than the risk of performing a DSA. Aksoy and colleagues (2000) raised the question of whether MRA should be part of the diagnostic work-up of these pa-

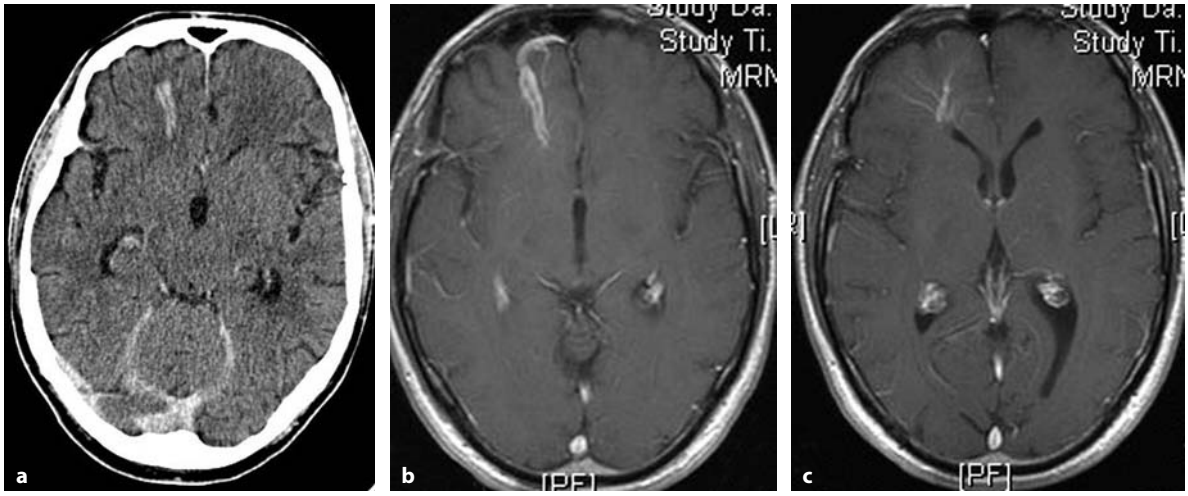


Fig. 1.15a–c. Contrast enhanced CT showed two parallel transcerebral veins, the medullary veins were not seen on 10-mm slices, T1 weighted with contrast delineate the typical structure of a DVA

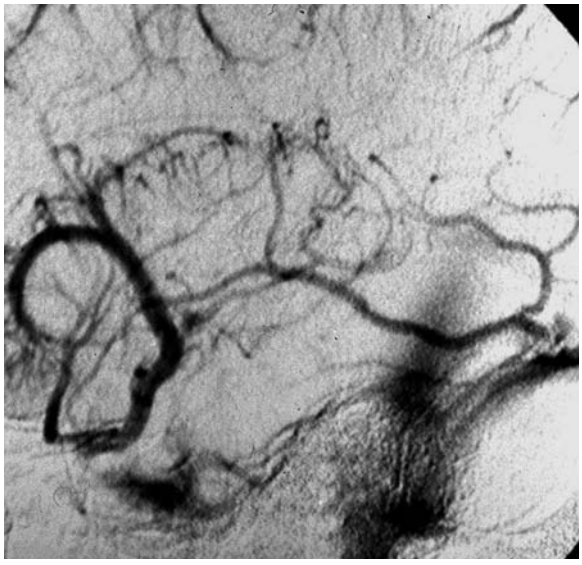


Fig. 1.16. Digital subtraction angiography (lateral view) of a developmental venous anomaly located in the right temporal lobe. Note the typical upside-down umbrella shaped transcerebral draining vein

tients. Again, it is not necessary in a typical DVA and it can be helpful in an atypical one.

Boukobza et al. (1996) found a specific pattern of DVAs in patients with extensive venous malformations of the head and neck. The draining veins were more tortuous and dilated and more often draining into the deep venous system. Additionally, the incidence of DVA seems to be increased in patients with slow-flow vascular malformations of the head and neck. In their series of 40 patients with head and neck venous malformations, 8 had intracranial DVAs and 5 multiple DVAs. In the literature, multiple DVAs have been reported to occur in around 25% of cases, sometimes related to other congenital disorders and syndromes (Rigamonti et al. 1987; Rigamonti and Spetzler 1988).

In conclusion, patients with head and neck venous malformations obviously have an increased probability of having a DVA and an increased chance of having multiple DVAs. There are no data on whether the risk of having cavernomas is also increased in this patient subgroup.

However, multiple DVAs are associated with at least one, sometimes even more than one, cavernoma (Figs. 1.8 and 1.9).

1.4 Therapy

In earlier literature (Cabanes et al. 1979; Handa et al. 1984; Lobato et al. 1988; Lupret et al. 1993; Malik et al. 1988; McCormick et al. 1968; Moritake et al. 1980; Sadeh et al. 1982; Sarwar and McCormick 1978), you will find authors recommending surgical resection of DVAs, assuming the lesion is accessible and symptomatic, e.g., presenting with hemorrhage. According to more recent literature (and what you read on the previous pages), the DVA is a functional

venous channel draining normal parenchyma and the risk for venous infarction after surgery or radiosurgery is high (Fig. 1.17). In fact, resection of the vein is associated with unacceptable morbidity and mortality (Biller et al. 1985; Meyer et al. 1995; Pak et al. 1980; Sadeh et al. 1982; Senegor et al. 1983). Martin et al. (1984) reported an episode of severe cerebellar swelling even with only temporary occlusion of the visualized draining veins requiring abortion of the operation. Similarly, radiosurgery of DVAs has a 30% complication rate, can lead to venous infarction, and nearly never leads to total venous obliteration. With the knowledge of the indolent and benign natural history of DVAs in general, McLaughlin and colleagues recommended observation as the primary mode of strategy. In the case of hemorrhage – assuming that the bleeding is caused by an associated cavernoma – they recommend simple clot removal with preservation of the vein (Fig. 1.5). The surgeon should be alert to finding a cavernoma associated with the DVA, but the DVA itself is a "leave-me-alone" lesion.

We are not really convinced by the recommendations of McLaughlin and colleagues regarding pure DVA and the need for observation. If there is an adequate MRI examination, excluding a cavernoma with the highest possible probability, We would not (and in fact we don't) recommend any follow-up or observation of a patient with just a DVA. It's hard to explain that it is just a variant – and not a disease – but needs observation over time. Our recommendation and explanation to the patient and/or the referring doctor is that it usually needs no observation, the bleeding risk is not increased, and the problem for referral is not related to the DVA.

However, if the DVA is associated with a cavernoma, the therapeutic implications are related to the cavernoma. The difference is the surgical approach: in a pure cavernoma, the goal is to remove the whole cavernoma including the hemosiderin rim. If associated with a DVA, the draining vein has to be preserved and, therefore, sometimes the cavernoma cannot be removed totally.

A final remark to those patients with an incidental finding of a DVA: patients are not restricted in any way from normal daily activities or from pregnancy!

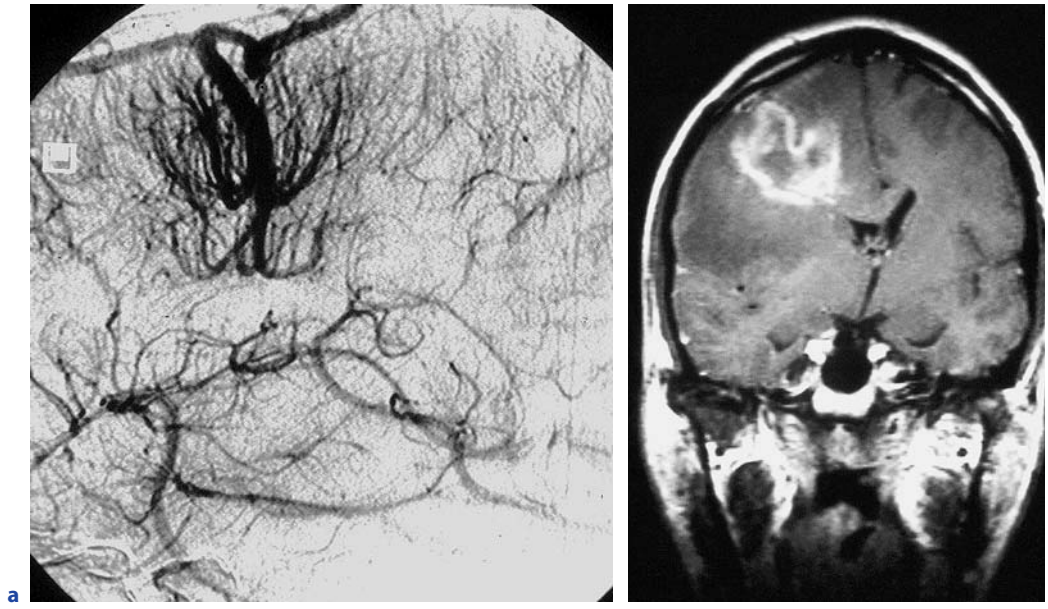


Fig. 1.17. a Digital subtraction angiography of an unusual large developmental venous anomaly of the right hemisphere. Note the doubled upside-down umbrella with two Medusa heads and a single transcerebral draining vein. For unknown reasons, the patient received stereotactic radiation therapy and came back to the hospital 9 months later. **b** The magnetic resonance image at that time revealed a massive hemispheric swelling due to a large venous infarction after radiation-induced thrombosis of the collector vein

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Cavernomas and Capillary Telangiectasias

2

Wilhelm Küker and Michael Forsting

CONTENTS

KEY POINTS

- Cavernomas are endothelium lined sinusoidal blood cavities without other features of normal blood vessels like muscular or adventitial layers. No brain tissue is present between the blood cavities
- Cavernomas may occur sporadically, after radiation, or hereditarily following an autosomal dominant trait
- The majority of cavernomas present with seizures
- Annual bleeding rate of cavernomas ranges between 0.25% and 0.7% per year
- During follow-up of cavernomas, progression in size can occur which is related to osmotic changes
- Cavernomas may be calcified and have a typically pop-corn like appearance on MRI
- Surgical resection is recommended for cavernomas presenting with symptomatic hemorrhage in accessible and non-eloquent locations
- Capillary telangiectasias are composed of multiple thin-walled vascular channels between normal brain parenchyma
- Diagnosis of capillary telangiectasias is made with MRI. Non-specific symptoms may be associated, tinnitus being more common
- Therapy and follow-up of capillary telangiectasias is not necessary

2.1 Cavernomas

Crawford and Russell (1956) first coined the term "cryptic" vascular malformation in reference to small, clinically "latent vascular lesions", that resulted in either apoplectic cerebral hemorrhage or signs of growing mass lesion. Most of these vascular malformations were angiographically occult.

Voigt and Yasargil (1976) gave a first overview of the entity of intracerebral cavernomas. At that time, these malformations were thought to be rare. Since then, diagnostic modalities have changed dramatically: not only has computer tomography (CT) become available, but magnetic resonance imaging (MRI) has proved to be the most sensitive diagnostic tool for cavernomas. And thanks to MRI, our knowledge about cavernomas has increased since 1976; there remain, however, several question marks associated with these malformations. During the last years research has in fact caused some more confusion: an increasing number of authors believe

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that cavernomas are an acquired lesion instead of congenital and that at least changes any calculation of bleeding risk (Campeau and Lane 2005; Sure et al. 2005).

2.1.1 Pathology

Vascular malformations of the brain are usually divided into arteriovenous malformations, capillary telangiectasias, venous malformations, and cavernous malformations. However, for a long time, the term "angiographically occult vascular malformation" or "cryptic" (Cohen et al. 1982; Dillon 1997; Wilson 1992) has been used to describe those vascular malformations that could not be visualized angiographically, but obviously were able to cause intracerebral hemorrhage.

Cavernomas, also called cerebral cavernous malformations or cavernous hemangiomas, are characterized by endothelium lined, sinusoidal blood cavities without other features of normal blood vessels like muscular or adventitial layers (Fig. 2.1) (McCormick et al. 1968).

The diameter of the blood vessels lies within the range 30–50 μm. No brain tissue is present between the blood cavities, which are embedded into connective tissue. This is from a histopathological point of view the major difference between cavernomas and capillary telangiectasias. In the latter, there is intervening brain parenchyma between the vascular channels. However, since Rigamonti et al. (1987, 1988) found more than 30% incidence of intervening brain parenchyma in more or less typical cavernomas, there is an ongoing debate whether cavernomas and capillary telangiectasias simply represent two pathological extremes within the same vascular malformation category. The suggestion is to group them in an entity called "cerebral capillary malformation". This new way of looking at cavernomas and capillary telangiectasias is clearly of interest from an academic point of view. From a clinical point of view, it still seems reasonable to us to maintain the established classification.

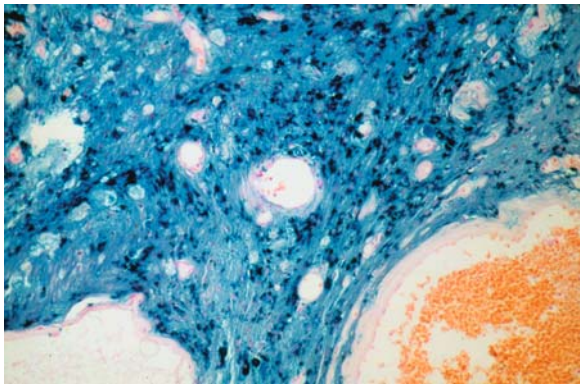

Fig. 2.1. Histology of a typical cavernoma with endothelium-lined, sinusoidal cavities without other features of normal blood vessels, such as muscular or adventitial layer

Cavernomas are not encapsulated, but well separable from brain parenchyma. However, the surrounding brain usually exhibits evidence of prior microhemorrhage, hemosiderin, discoloration, and hemosiderin-filled macrophages (Maraire and Awad 1995; Russel and Rubinstein 1989). This indicates recurrent microbleedings or leakage of red blood cells. Thrombi of varying age are characteristic and are present within many of the vessels. Calcification (Fig. 2.2) and surrounding gliosis typify the margins of the lesion.

During follow-up, expansion of cavernomas can occur, but this is mainly related to osmotic changes or differences (as in chronic subdural hematoma).

Regarding the problem of active growth, there has been a lot of discussion during the last few years (Rivera et al. 2003). Initially, all cavernomas were thought to be congenital. There is now evidence that cavernoma can arise de novo. Known factors promoting de novo formation are previous irradiation (Nimjee et al. 2006), genetics in familial cases, viruses, hormonal influences in pregnancy and local seeding along a biopsy tract. In a recent paper (Lehnhardt et al. 2005), de novo cavernomas in serial MRIs in patients with familial cavernomas were confirmed. Repeated intralesional microhemorrhages and their breakdown products can also initiate a series of responses such as cellular proliferation and fibrosis that promote new vessel formation and hemorrhagic angiogenic proliferation. Radiation-induced cavernous hemangiomas (RICH) are rare complications of cerebral irradiation. The mechanism underlying the induction of cerebral cavernous malformations by cerebral irradiation (CI) is not clear. RICH appear to be more prevalent among females (Gaensler et al. 1994; Larson et al. 1998). The interval between radiotherapy and the diagnosis ranges between 2 and 23 years and there appears to be a dose-response relationship in the few reported cases (Ciricillo et al. 1993; Novelli et al. 1997; Wilson 1992). With the improvement in survival for cancer patients, RICH are increas-

ingly diagnosed as an incidental finding on control MRI. Because the hemorrhagic potential of RICH is not documented, no guidelines exist regarding the treatment of such an occurrence (Poussaint et al. 1995). Duhem et al. (2005) published a series with nine patients developing a cranial cavernoma after irradiation and found that among the nine cases bleeding was documented in five cases and was significant enough to warrant surgical evacuation in three. This 55.6% bleeding rate suggests that RICH might be more hemorrhage-prone than spontaneously occurring cavernomas (Robinson et al. 1991). The pathogenesis of RICH is unclear, and two hypotheses have been proposed: the first surmises that the cavernoma was present, but radiographically occult, before irradiation, and that irradiation induces its growth. The second model proposes that the cavernoma developed de novo in response to radiotherapy (Duhem et al. 2005; Larson et al. 1998). Radiation-induced vascular changes include dilatation and proliferation of the endothelium, with fibrinoid necrosis and hyalinization of vessel walls and formation of telangiectasia (Gaensler et al. 1994). Radiation-induced vascular changes could cause repeated hemorrhage and thrombosis, leading to a cascade of events that includes cellular proliferation, angiogenesis, and fibrosis.

Another more recent paper dealing with the development of cavernous hemangiomas of the brain following radiation therapy was written by Baumgartner et al. (2003). What they found is that patients treated with lower doses of whole-brain radiation therapy developed symptomatic cavernous hemangioma later than did those treated with higher doses of whole-brain radiation therapy. In their study, the patient who received radiation therapy at the youngest age developed more lesions than did the other two patients. Their hypothesis is that the younger brain is more susceptible to the development of multiple radiation-induced cavernomas. Anderson suggests a 4.8% incidence rate of cavernoma development, appearing a mean of 5.5 years after radiation therapy. They finally conclude that radiation-induced cavernomas appear 7–19 years after radiation therapy, slowly enlarge, and become symptomatic 9–19 years after radiation therapy. Pathologically, radiation-induced cavernomas are identical to sporadic and familial cavernomas.

Most of the de novo cavernoma reported belong to the familial form of the disease, with an incidence of 0.2–0.4 lesions/patient-year (Brunereau et al. 2000a,b). The question still is whether these new lesions are simply previously undetected radiologically, or do they represent a true pathologic angiogenesis. (Desal et al. 2005).

The sinusoidal walls may be locally thickened or hyalinized with spots of calcification. The structure of the sinusoidal walls is a unique feature of cavernomas.

The cavity of the dilated vessels may contain clotted blood in different stages of degradation. Ultrastructural examinations have disclosed a lack of tight junctions in the wall of cavernomas (Wong et al. 2000). The known propensity for growth and bleeding of cavernomas has been attributed to this rarity of tight junctions, as well as to the lack of significant subendothelial support. However, the precise reason for a macroscopic hemorrhage in these low-flow malformations without any elevated intralesional blood pressure is unclear. Recently, Tu et al. (2005) demonstrated that the vascular walls of cavernomas do not have basement membranes and astrocytic foot processes.

The macroscopic appearance of cavernomas can be described as mulberry-, grape-, or popcorn-like with a diameter up to several centimeters.

Cavernomas may occur sporadically (Kupersmith et al. 2001), after radiation therapy (Amirjamshidi and Abbassioun 2000; Olivero et al. 2000), and hereditarily (Labauge et al. 1998) following an autosomal dominant trait. Recently, genes causing cavernomas were mapped on chromosomes 7q, 7p, and 3q in a group of families. The CCM1 locus on chromosome 7q21–22 harbors the Kritl gene, which probably encodes a tumor suppresser protein (Zhang et al. 2000; Davenport et al. 2001). The occurrence of sporadic cavernomas may be due to the functional loss of the CCM1 gene in heterozygous individuals. Further disease loci (CCM2 on chromosome 7pl3–15 and CCM3 on chromosome 3q25.2–27) have been found in other families; however, the genes have not yet been identified. Although genetic causes have been detected in familial forms of the disease, for the majority of sporadic cases the genetic contribution remains to be determined. However, because all first-degree relatives of patients with cavernomas may not be screened radiographically, the ratio of true sporadic to familial cases may be underestimated. Beside the autosomal transmission, the hallmark of the familial form is multiplicity of cavernomas within the brain (Brunereau et al. 2000a,b).

The incidence of the familial form seems to be particularly high in individuals of hispanic descent (Rigamonti et al. 1988; Zabramski et al. 1994).

Causal mutations have been demonstrated in three genes, KRIT1, MGC4607, and PDCD10, but additional genes are likely to be discovered. These genes are therefore thought to play a role in angiogenesis. Their specific modes of actions, their contribution to and their likely penetrance in the genesis of CCM are the subject of current investigations. Genetic counselling is strongly advisable for patients with a positive family history and for seemingly sporadic cases with multiple lesions, and genetic testing should be considered on an individual basis. The identification of a mutation enables precise genetic testing of relatives. Given the 50% a priori risk of autosomal dominant inheritance, the benefits of genetic testing are twofold: a positive test result in a presymptomatic carrier permits close neuroradiological surveillance and timely neurosurgical intervention; a negative test result relieves the proband of unwarranted anxiety and unnecessary medical supervision (Felbor 2006).

The question as to why cavernomas predominantly occur in the central nervous system (CNS), as well as in the spinal cord, skin, and eyes (Sarraf et al. 2000), is still unresolved. Other, rare locations include the cerebral ventricles (Reyns et al. 1999), cranial nerves (Ferrante et al. 1998), the cavernous sinus (Bristot et al. 1997), or subarachnoid space (Kim M et al. 1997). There are also reports on an extradural location (Porter et al. 1999).

Cavernomas are frequently accompanied by developmental venous anomalies (see Fig. 2.13) (see Chap. 1). According to some reports, brainstem cavernomas are often associated with a venous abnormality (Porter et al. 1999). This has led to speculation that an impaired venous drainage may have caused the dilatation of capillary channels. This theory is supported by another rare finding: some authors found recurrence after surgical removal on a cavernoma just in those patients in which the associated DVA was not touched! (Wurm et al. 2003). They suggested occluding at least small venoles around the cavernoma in order to prevent recurrence of the cavernoma. Up to now this is the opinion of a minority. However, it is true what Mark Twain said: "The man with a new idea is a crank until the idea succeeds".

Finally, the pathologic descriptions of all cryptic vascular malformations have been and are still confusing. Mixtures of two and more vascular malformations within the same histologic specimen have been identified by a few authors (Awad et al. 1993; Chang et al. 1997; Herata et al. 1986). Wilson (1992) reported on 73 cryptic vascular malformations and classified them into cavernous angiomas, cryptic vascular malformations with arterial components, or cryptic or thrombosed arteriovenous malformations (AVMs). In addition, 40% of all cryptic vascular malformations were characterized as thrombosed AVMs. From a radiological point of view, true AVMs have an extremely low tendency towards spontaneous thrombosis, so this entity is a rare finding.

In summary, there are many conflicting reports and interpretations in the literature regarding pathological classification of these "cryptic malformations". It is our opinion that classification of vascular malformations in the majority of patients should be done on the basis of radiological findings. Pathologists usually receive incomplete fragments of tissue, do not know the hemodynamics within the lesion, and mostly are unaware of the radiologic findings. This is the major reason for the inconsistency that characterizes pathologic reports of cryptic malformations.

2.1.2 Clinical Presentation

There is no reliable study giving us an exact idea of the incidence and prevalence of cavernomas; nevertheless, to get some knowledge about the available data, the prevalence has been estimated on the basis of autopsy or MR imaging to be 0.5%–0.7% (Del Curling et al. 1991; Robinson et al. 1991). The incidence of cavernomas has been estimated to be in the range between 0.4% and 0.9%; cavernomas account for 8%–15% of all intracranial vascular malformations (Porter et al. 1999; McCormick and Nofzinger 1966; Del Curling et al. 1991; Kim DG et al. 1997). Over the last two decades, incidence data have been confirmed by MRI-based retrospective studies (Robinson et al. 1991; Del Curling et al. 1991). There is no male or female preponderance and up to 25% of all cavernomas are found in the pediatric population. As much as 60% of lesions are superficial, 30% are deep (brainstem, cerebellar nuclei, basal ganglia, thalamus), and 3% are within the spinal cord.

Multiple cavernomas occur in up to 90% of familial cases and in around 25% of sporadic cases (Clatterbuck et al. 2000; Labauge et al. 2000). Therefore, whenever a single cavernoma is detected on MRI, one has to look for multiple lesions.

On average, 20% of cavernomas occur in the posterior fossa and 80% are seen supratentorially. However, the range given for brainstem cavernomas is 9%–35% (Porter et al. 1999; Kupersmith et al. 2001). Spinal cord and extra-axial cavernomas are relatively rare and account for around 5% of all lesions (Clatterbuck et al. 2000). There is a single case report about multiple spinal cavernomas after irradiation to the chest and abdomen for a Wilm's tumor during childhood (Jabbour et al. 2004). However, spinal cavernomas do occur more often in the familial form than sporadic and about 50% of patients with spinal cavernomas do have at least one additional lesion in the brain (Cohen-Gadol et al. 2006). These findings support the need for complete neuraxis imaging in patients with a diagnosis of spinal cavernomas, irrespective of family history, to exclude the presence of a similar intracranial lesion.

The average size of cavernomas is between 15 and 19 mm (Kim DG et al. 1997; Robinson et al. 1991). However, only 10% of lesions remain stable over time: 35% increase and 55% decrease during a mean follow-up of 2 years (Clatterbuck et al. 2000). This dynamic behavior is on the one hand related to recurrent bleedings and resorption of blood products, while on the other hand related to osmotic changes (Zabramski et al. 1994). However, according to recent reports there is a small subgroup with de novo development of cavernomas.

Patients with cavernomas present with a variety of symptoms. Seizures are reported as the most common symptom, accounting for 38%–55% of patient's complaint (Del Curling et al. 1991; Robinson et al. 1991; Simard et al. 1986; Brunereau et al. 2000a,b). Other symptoms include focal neurologic deficits in 12%–45% of patients, recurrent hemorrhage in 4%–32%, and chronic headaches in 5%–52%. Brainstem cavernomas (see Figs. 2.3, 2.4, 2.7, 2.15 and 2.16) nearly never cause seizures! Most of these patients do have typical brainstem symptoms like diplopia, face or body sensory disturbances, or ataxia. Without imaging, this subgroup of patients with infratentorially located cavernomas can closely mimic the clinical picture of multiple sclerosis.

The majority of patients become symptomatic between the third and fifth decade, and there is no definite association between symptoms and gender. The frequency of asymptomatic cavernomas is not precisely known, but according to the reports of Zabramski et al. (1994) and Brunereau et al. (2000a,b) it seems to be as high as 40%.

2.1.2.1 Hemorrhage

The central clinical and therapeutic problem in patients with cavernomas is the question of hemorrhage. On a first view, this should be a simple question with a simple answer. However, both assumptions are wrong. The problem starts with the definition of a hemorrhage and ends with individual answers for each patient.

On one side, hemorrhage can be defined clinically: first or sudden onset of new neurologic symptoms in a patient with a cavernoma is usually related to a new or first hemorrhagic event. But looking into the literature, you will find an amazing number of different descriptions and terms to describe cavernoma-related hemorrhages: overt hemorrhage, symptomatic hemorrhage, gross hemorrhage, microhemorrhage, intralesional or perilesional ooze or diapedesis, clinically significant hemorrhage, subclinical hemorrhage, and others (Aiba et al. 1995; Kondziolka et al. 1995b; Robinson et al. 1991; Karlsson et al. 1998). The reason for this variety of descriptions is the fact that on one hand clinical events alone were used to define hemorrhage and on the other hand different imaging modalities (mainly MRI) had a major impact on the definition of hemorrhage. In Section 2.1.3, we recommend the use of the established Zabramski classification in order to allow comparison of different patient groups and studies. However, the problem in defining a hemorrhage is a major reason for the still ongoing debate about the risk of hemorrhage and bleeding rates in patients with cavernomas. Most estimations assume that cavernomas are present from birth and risk of hemorrhage and bleeding rates are mainly based on that assumption. Del Curling et al. (1991) and Robinson et al. (1991) were the first to calculate the annual hemorrhage rate and figured out that it ranges between 0.25% and 0.7% per patient per year. Aiba et al. (1995) analyzed their group on the basis of the initial finding: if bleeding was the initial symptom, the annualized hemorrhage rate was 22.9%; if seizures were the first symptom, the bleeding rate was calculated to be 0.39% per patient per year. Kondziolka et al. (1995b) also stratified their patient group into those who had previously experienced a hemorrhage and those who had not. Patients with one previous hemorrhage had an annual 4.5% risk of hemorrhage, whereas those without a previous hemorrhage had a 0.6% annual risk. An analysis of the symptomatic bleeding risk in untreated

patients who had already experienced two or more hemorrhages found the rate to be approximately 30% per year (Kondziolka et al. 1995a). Other authors, usually not differentiating between initial symptoms, published hemorrhage rates between 1.1% and 3.1% (Zambramski et al. 1994; Moriarity et al. 1999). Porter et al. (1999) reported that brainstem cavernomas might have a significant increased risk of hemorrhage and calculated it with 5% per person per year. In contrast, Kupersmith et al. (2001) found a bleeding rate of 2.46% in brainstem cavernomas. However, the rebleeding rate – and this is quite well supported by other data – seems to be beyond 5% in brainstem cavernomas. All studies suggest that the occurrence of a rebleeding is an indication of a higher bleeding probability of a given cavernoma. The risk of a symptomatic rebleed at least doubles in comparison to asymptomatic cavernomas (Kupersmith et al. 2001). These findings clearly should have an impact on therapeutic decisions. The bleeding incidence is higher in patients with the inherited form of cavernomatosis – not for a single given cavernoma, however, but in terms of patient years (Labauge et al. 2000).

Patients younger than 35 years of age experienced more bleeding episodes and the same was true for those with cavernomas of at least 10 mm. A number of studies addressed the increased bleeding risk among women (Robinson et al. 1991; Aiba et al. 1995; Moriarity et al. 1999); the majority of studies, however, did not find any gender difference in bleeding risks. Other authors figured out that the most significant predictor of clinical events is lesion location. The annual event rates are 6.5% for infratentorial and 0.7% for supratentorial lesions. Following another classification (deep vs superficial) deep lesions do have a significant higher bleeding incidence. Intuitively, the most plausible explanation for that is that the eloquence of deep structures will lead to clinical symptoms even with a small change in size of the lesion. Differences in venous pressures between deep and superficial neural tissue might be another reason for the higher hemorrhage rate in deep lesions. On the basis of the former theory, the functionally important and closely packed pathways of the spinal cord most likely allow manifestation of clinical event with smaller cavernoma hemorrhages. However, Cohen-Gadol et al. (2006) found an event rate of 1.6% per patient per year, which is more similar to the rates for cerebral cavernoma than for brainstem cavernoma, despite the analogous eloquence of the spinal cord and brainstem. This difference may be explained by structural or venous drainage variations (that is a lack of clear association with DVA) that prevent lesional rehemorrhage in the spinal cord.

The main problem in all these studies is a substantial selection bias and the definition of hemorrhage. Another, but probably more important, aspect for patients when discussing bleeding risks is the clinical significance of hemorrhage and the probability of a good recovery. The probability of a fatal hemorrhage is low and many patients do show a complete or nearly complete recovery after the initial bleeding. The initial bleed causes an only transient deficit in 80% of the patients. However, with each subsequent hemorrhage there is an increased chance of the patient ending up with a relevant deficit. Usually, patients with more than two hemorrhages from the same lesion will have a persistent neurologic deficit. Deep lesions have a lower probability of full recovery after bleeding than do superficial lesions. In general, bleeding rates given by surgical groups tend to be higher than those observed by others.

Finally, with regard to the risk of a cavernoma to the patient, the majority of data in the literature calculate an annual risk of 0.5%–1% of symptomatic hemorrhage (which is much lower than in true AVMs) and a low risk of fatal hemorrhage (Moran et al. 1999). In the majority of patients, particularly those over 35 years of age, suffering from a single cavernoma below 10 mm in size and with seizures as the initial symptom, a wait-and-see strategy seems to be reasonable. In patients presenting with an initial hemorrhage, the repeat hemorrhage risk seems to be much higher, particularly if more than one bleeding event has already occurred.

2.1.2.2 Seizures

As mentioned above, the majority of patients with cavernomas present with seizures as initial symptom (Moran et al. 1999). It is important to know that in the vast majority of patients these seizures are not related to acute bleeding events, but to hemosiderin deposition adjacent to neurons. Hemosiderin or ferritin is a well-known epileptogenic agent (at least in animal experiments). Being aware of the relation between seizures and hemosiderin deposition is of particular importance if surgical removal of the cavernoma is considered due to conservative untreatable seizures. It is of utmost importance not only to remove those parts of the cavernoma with

obvious cavernoma, but also to remove the hemosiderin deposits around the cavernoma within the adjacent brain tissue (Baumann et al. 2006). This part of the malformation is probably responsible for the seizure (see Figs. 2.8 and 2.17).

However, this hemosiderin-removal dogma is under discussion. Experience shows that 30%–50% of patients with a cavernoma having seizures can become seizure-free after radiation therapy, so hemosiderin as the only causative seizure agent has to be re-discussed (Hsu et al. 2007; Liu et al. 2005). Pure lesionectomy without removal of surrounding hemosiderin deposits have also been shown to reduce seizures effectively (Ferroli et al. 2006). Several groups figured out that early medical therapy after onset of seizures is more important than the resection procedure per se. In patients with a short seizure history or few pre-op seizures, lesionectomy alone may be enough. A longer history on the other hand might require a more extensive resection (Hammen et al. 2007).

2.1.2.3 Headache

Headache is a frequent reason for submitting a patient to imaging. Therefore, there are always discussions whether an incidental finding like an arachnoid cyst, a small meningioma or – more relevant for this chapter – a cavernoma might be the cause of the patient's headache. However, the first and most important question is: What type of headache does the patient have? If this is a clinically typical migraine, a typical tension headache, or any other easy-to-define type, the headache is usually not related to the cavernoma. In our personal experience, there are some patients, suffering from recurrent attacks of a severe, subarachnoid hemorrhage (SAH)-like headache with cavernomas at the surface of the brain. Since these cavernomas may have contact to the subarachnoid space, micro-bleeds might cause headache attacks like in a SAH (warning-leak headache). Postural intermittent headache might be the initial symptom if the cavernoma is located in the third ventricle, although a very rare location for a cavernoma.

2.1.2.4 Focal Neurologic Deficits

Focal neurologic deficits like transient speech arrests, sensomotoric deficits, ataxia, visual disturbances, or eye movement disorders are nearly always related to the location of the cavernoma and hemorrhages. There are no steal mechanisms in cavernomas (this is different in AVMs), nor are there any venous overload problems.

2.1.3 Diagnostic Imaging

Due to the slow blood flow, usually cavernomas are angiographically occult vascular malformations. If the lesion has hemorrhaged, an avascular area with moderate mass effect can sometimes be identified. Occasionally – in less than 10% of cases – a faint blush on the late capillary or early venous phase of high resolution angiograms can be seen (Savoiardo et al. 1983). Angiography is rarely necessary in typical cavernomas. If associated with a DVA, presurgical digital subtraction angiography (DSA) may be indicated to analyze the venous drainage pattern. The same is true for those cavernomas which do not have the typical MR appearance. In some of these, DSA can increase the diagnostic confidence.

On CT, and even more so on MRI, features are more or less pathognomonic. Whereas large cavernous hemangiomas can be visible on CT, small lesions are only visible on MRI.

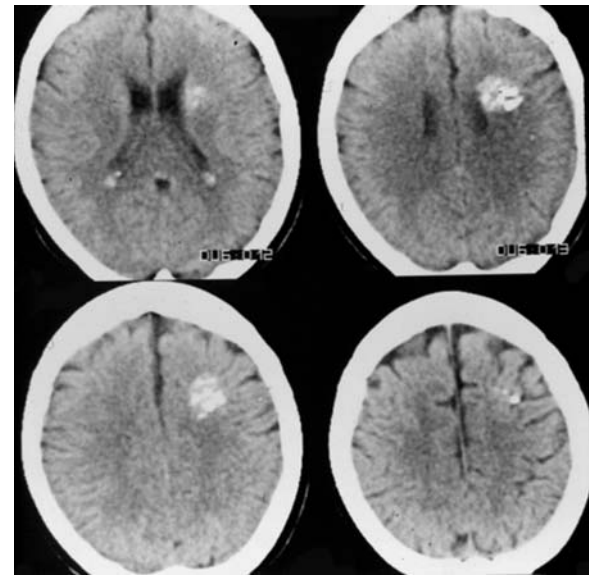

Fig. 2.2. CT of a typical, partially calcified cavernoma adjacent to the left ventricle. The missing mass effect (no compression of the ventricle, normal width of the external cerebrospinal-fluid space) is a striking argument against a true tumor (like oligodendroglioma)