
Cerebral Vasculitis

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Abstract

Vasculitis is an inflammation of blood vessels due to various origins. Vessels of the peripheral and/or central nervous systems may be involved. Clinical and radiological diagnosis of cerebral vasculitis is challenging as there is no vasculitis-specific symptom or imaging sign. Furthermore, it may mimic other neurological diseases, which would require different treatment approaches. Neuroimaging of cerebral vasculitis should begin with initial MRI to assess the degree of parenchymal damage and to detect vessel wall changes. If the results are indefinite DSA should be pursued in order to detect potential changes of medium-sized vessels. Vasculitides of small vessels cannot be detected by vascular imaging and require brain or leptomeningeal biopsy.

1 Epidemiology, Clinical Presentation and Therapy

Christian Jacobi and Brigitte Wildemann

Summary

Vasculitis is defined as inflammation of blood vessels with or without necrosis of the vessel wall. Vasculitis can be further classified based on the origin of vessel pathology into immunoallergic, infectious and neoplastic forms, and divided into primary and secondary subtypes. To confirm the diagnosis, histology is usually required. Vasculitis may involve vessels of both the peripheral and central nervous systems (CNS). Vasculitis of the CNS is rare and occurs in the context of systemic diseases or as primary angiitis of the CNS. The clinical diagnosis of CNS vasculitis is difficult, as there is a wide spectrum of neurological signs and symptoms, and specific technical examinations to confirm the CNS manifestation do not exist.

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Table 1 Examples for primary and secondary vasculitis affecting the nervous system

<i>Primary vasculitis</i>
Churg–Strauss syndrome
Polyarteritis nodosa
Microscopic polyangiitis
Wegener’s granulomatosis
Takayasu arteritis
Hypersensitivity vasculitis
Cryoglobulin-associated vasculitis
Primary vasculitis of the central nervous system
<i>Secondary vasculitis</i>
Connective tissue diseases and other systemic autoimmune diseases
Sjögren syndrome
Rheumatoid arthritis
Systemic lupus erythematosus
Mixed connective tissue disease
Behçet’s disease
Infections (e.g. HIV, CMV, spirochetes)
Neoplastic diseases (e.g. lymphoma, solid tumours)
Drug exposure (e.g. morphine, cocaine)

1.1 Classification

Cerebral vasculitis can be classified in different ways. One classification is based on the differentiation between primary and secondary subtypes (Table 1).

Primary vasculitis can be further classified depending on the size of the affected vessels (small, medium, large). The international consensus classification (Chapel Hill classification from 1994) defines the vessel size depending on the smallest affected vessel. Other classifications include histological (e.g. granulomas) and immunological markers (e.g. the association with antineutrophil cytoplasm antibodies, ANCA).

1.2 Epidemiology

The overall incidence of primary vasculitis is about 40/1,000,000 persons [excluding giant cell (temporal) arteritis, GCA]. Its incidence increases with age. The incidence of GCA is much higher (around 200/1,000,000 persons in the age group >50 years).

The frequency of CNS manifestations in primary vasculitis is not well examined. Published data exist for polyarteritis nodosa (10–40 %), Wegener’s granulomatosis (10 %) and Churg–Strauss syndrome (10 %). In all other primary vasculitides CNS manifestations seem to be rare.

In secondary vasculitis valid data as to the frequency of CNS involvement are not uniformly available. CNS vasculitis is reported in around 5 % of cases in Sjögren syndrome and in 10–30 % of patients diagnosed with mixed connective tissue diseases. In systemic lupus erythematosus CNS involvement affects 40–60 % of patients but is attributable to vasculitis in 7–13 % of cases only. The frequency of neuro-Behçet is around 10–40 %.

1.3 Clinical Presentation

Clinical and pathological presentation in CNS vasculitis represents a wide spectrum. Among others, headache, cranial nerve affections, encephalopathy, seizures, psychosis, myelitis, stroke, intracranial haemorrhage and aseptic meningoencephalitis are described.

Aside from clinical examination (comprehensive clinical history and clinical examination), the diagnosis of vasculitis requires multiple technical examinations: laboratory tests (blood cell count, erythrocyte sedimentation rate (ESR); clinical chemistry panel [including C-reactive protein (CRP), liver and renal functions], anti-double stranded (ds) DNA, antinuclear antibody (ANA) and, if positive, ANA fine specificities (anti-Sm, anti-SSB, anti-SSA, antihistone, anticentromere, anti-Scl70, anti-nRNP, anti-Jo-1, anti-PM-Scl), ANCA, complement (C3 and C4) and cryoglobulin levels, rheumatoid factor, immunofixation electrophoresis, quantitative immunoglobulins, lupus anticoagulant (LA), anticardiolipin antibody (aCL), serology for hepatitis B and C virus) as well as radiographic examinations (e.g. CT, MRI, PET and SPECT). In case of suspected CNS involvement, electrophysiological studies, such as electroencephalography and evoked potentials, may be helpful. CSF analysis is another powerful tool to detect CNS involvement. Pleocytosis and intrathecal immunoglobulin synthesis are the most prominent abnormalities; however, these abnormalities are non-specific. The gold standard to diagnose CNS vasculitis remains the histopathological examination of affected organs.

In the following sections selected primary and secondary vasculitides leading more frequently to CNS manifestations are discussed in more detail.

1.3.1 Primary Vasculitides

1.3.1.1 Large-Vessel Vasculitis

Giant Cell (Temporal) Arteritis

Giant cell (temporal) arteritis (GCA) involves the ophthalmic, posterior ciliary, superficial temporal, occipital, internal maxillary and facial arteries. In around 20 % of cases it is associated with polymyalgia rheumatica. Initial symptoms are exhaustion, myalgia, fever and weight loss.

The patients complain of parietal headache and visual disturbances. The temporal artery is often tender to touch. During the course of disease the temporal artery gets thicker and loses its pulse. Ptosis and diplopia, due to ischaemia of the extraocular muscles and claudication of the jaw, are other possible symptoms. In some cases ischaemia of the tongue and scalp may arise. Diagnostic criteria of the American College of Rheumatology (ACR) are defined and include the following (positive if at least three are present):

1. Age at disease onset >50 years
 2. Blood sedimentation reaction >50 mm/h (first hour)
 3. New headache
 4. Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
 5. Typical histology in temporal artery biopsy
- Untreated GCA can lead to visual loss.
Rarely GCA affects intracranial vessels and may cause transient ischaemic attacks (TIA) and stroke.

Takayasu Arteritis

Takayasu arteritis is a granulomatous vasculitis of the great elastic branches (aorta and its major extracranial vessels, pulmonary arteries). It usually affects young patients <40 years and is more common in women. Japanese and Mexicans are more frequently affected compared with Caucasians. The ACR criteria are defined as follows (positive if at least three are present):

1. Age at disease onset <40 years
2. Claudication of extremities
3. Difference of >10 mm Hg in systolic blood pressure between arms
4. Decreased brachial artery pulse
5. Bruit over the subclavian arteries or aorta arteriogram abnormality
6. Syncope is the most frequent neurological symptom; less common are TIA or stroke

1.3.1.2 Medium-Sized Vessel Vasculitis

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is commonly associated with viral infections (e.g. hepatitis B and C, HIV). In this necrotizing vasculitis medium and small vessels are affected. The first systemic symptoms are malaise, fever and weight loss. Skin lesions and renal involvement occur in up to 70 % of the patients and 45 % suffer from gastrointestinal symptoms. Laboratory examinations reveal increased ESR, CRP, decreased complement (C3 and C4) and circulating immune complexes. The most common neurological manifestation is peripheral neuropathy. The CNS involvement in PAN leads to headache, retinopathy and encephalopathy with seizures and cognitive decline (small-sized vessels). In around 10 % of the patients with neurological manifestations stroke and intracerebral haemorrhage are the leading CNS disorders

(medium-sized vessels). Other symptoms may arise from affection of the cranial nerves or the spinal cord.

1.3.1.3 Primary Angiitis of the CNS

Primary angiitis of the CNS (PACNS) is an isolated vasculitis of the central nervous system affecting small and medium-sized vessels in the brain and spinal cord. The most frequent clinical signs and symptoms (40–80 %) are chronic headache, encephalopathy and focal signs and symptoms (most frequently aphasia and hemiparesis). Stroke (ischaemia or intracerebral haemorrhage) is rare. The disease course is usually subacute (around 80 %) and may be relapsing or continuously progressive. Only in around 20 % of cases does the course fluctuate. CSF findings can be normal, but in most cases a pleocytosis can be detected during follow-up. The only possibility to confirm the diagnosis is a brain/leptomeningeal biopsy.

1.3.1.4 Small-Sized Vessel Vasculitis

Wegener's Granulomatosis

Wegener's granulomatosis affects the respiratory tract and the kidney with frequent glomerulonephritis. Usually anti-proteinase 3 (PR3, c-ANCA in around 90 % of the cases) can be measured in serum. The ACR defined the following diagnostic criteria for Wegener's granulomatosis (positive if at least two are present):

1. Development of painful or painless oral ulcers or purulent or bloody nasal discharge.
2. Urinary sediment showing microhaematuria or red cell casts.
3. Abnormal chest radiograph with the presence of nodules, fixed infiltrates or cavities.
4. Histological changes showing granulomatous inflammation within the wall of an artery or in the peri-vascular or extravascular area (artery or arteriole).

Stroke is a rare complication (4 %) of Wegener's granulomatosis. Intracranial granuloma following direct invasion from the nasal cavity may lead to an affection of the basal cranial nerves. Other possible neurological complications are aseptic meningitis, encephalopathy and sinus thrombosis.

1.3.2 Secondary Vasculitis in Connective Tissue Diseases

Connective tissue diseases, such as systemic lupus erythematosus (SLE), scleroderma, rheumatoid arthritis, mixed connective disease and Sjögren syndrome, are systemic immune-mediated diseases that lead to multiple organ affections. Diagnostic criteria for these diseases are defined by the rheumatological societies. A spectrum of antinuclear antibodies (ANA) is measurable in serum. In mixed connective disease, scleroderma, rheumatoid arthritis and Sjögren syndrome CNS manifestations are usually caused by

vasculitis, while in SLE vasculitis of cerebral vessels is rather uncommon and occurs in around 10 % of cases. The CNS involvement may cause headache, stroke (intracranial haemorrhage and ischaemia), sinus thrombosis, encephalopathy, seizures and aseptic meningitis. The CSF examinations often reveal a pleocytosis and intrathecal antibody synthesis including positive CSF oligoclonal bands.

1.3.3 Behçet's Disease

Behçet's disease usually affects the small blood vessels including arteries and veins. The major clinical signs are oral ulcers, genital ulcers, ocular lesions (mainly uveitis) and cutaneous involvement. CNS involvement is present in 10–40 % of patients and can be subdivided into parenchymatous (inflammation of the CNS tissue) and vascular neuro-Behçet. The most common neurological symptom of neuro-Behçet is headache. The parenchymatous manifestation leads to encephalitis and meningoencephalitis often affecting the basal ganglia and the brain stem. Possible vascular manifestations of neuro-Behçet include pseudotumour cerebri, sinus thrombosis and stroke. The CSF shows pleocytosis and intrathecal immunoglobulin synthesis and is usually normal in patients with pure vascular disease (e.g. sinus thrombosis).

1.4 Therapy

Vasculitis is a serious disease that is potentially fatal or leads to permanent disability and requires rapid institution of immunosuppressive treatment. Possible therapeutic options include glucocorticoids, cyclophosphamide, azathioprine, intravenous immunoglobulins and mycophenolate mofetil.

Systemic vasculitis with CNS involvement is usually treated with a combined medication of oral glucocorticoids (1 mg/kg prednisone) and oral cyclophosphamide as recommended by the modified Fauci scheme (2 mg/kg/day). It may be initiated by i.v. therapy with 1,000 mg methylprednisolone for 3 days. In severe cases a dosage of up to 4 mg/kg day cyclophosphamide may be required. In some cases plasmapheresis may be helpful. Following remission, long-term treatment can be continued with other immunosuppressants such as azathioprine, cyclosporine A, methotrexate or mycophenolatemofetil.

In GCA rapid treatment with oral glucocorticoids (e.g. 100 mg methylprednisolone for 2 weeks) is mandatory to avoid visual loss. After 2 weeks, slow reduction of steroids may be considered and tapering should be adjusted over many weeks.

Primary vasculitis of the central nervous system is treated with combined oral glucocorticoids (1 mg/kg prednisone) and oral cyclophosphamide (2 mg/kg/day). The therapy may be initiated with i.v. glucocorticoids (3 days 1000 mg methylprednisolone) followed by cyclophosphamid pulse

therapy before oral medication (Aksel S 2001; Berlit P 2004; Ferro JM 1998; Moore PM 1998).

2 Cerebral Vasculitis: Imaging and Differential Diagnosis

Martina Wengenroth

Summary

Vasculitides represent a heterogeneous group of inflammatory diseases that affect blood vessel walls of varying calibers (inflammatory vasculopathy). Cerebral vasculitis is defined as inflammation of leptomeningeal and/or parenchymal vessels of the brain. It is a rare but severe condition which can occur in all ages and often poses diagnostic challenges to clinicians and neuroradiologists alike. Clinically it can present with a panoply of manifestations such as headache, seizures, psychosis, and neurological deficits. In neuroimaging there is no vasculitis-specific sign and vasculitis may be mistaken for several other diseases such as multiple sclerosis, infections, or brain tumors, which all require different treatment approaches. Since the devastating symptoms of CNS vasculitis are at least partially reversible, early diagnosis and appropriate treatment are important. In order to establish a differential diagnosis clinical features, disease progression, age of onset, blood results, as well as CSF examinations have to be taken into consideration. Neuroimaging techniques, such as MRI and DSA, play a central role in the diagnosis and disease monitoring. The diagnostic protocol for cerebral vasculitis should include initial MRI to assess the degree of parenchymal damage and to detect vessel wall changes, in particular in large-vessel vasculitis. If the results are ambiguous or medium-sized arteries are affected (beyond the spatial resolution of MRI) DSA should follow. Small-vessel vasculitides entirely evade detection by vascular imaging and consequently require brain or leptomeningeal biopsy.

2.1 Neuroimaging of Cerebral Vasculitides

In cerebral vasculitis diverse causes may trigger leptomeningeal and/or parenchymal vessel wall inflammation of the brain. The term “arteritis” defines arterial inflammation, whereas “angiitis” is characterized by the inflammation of either arteries or veins. “Primary central nervous system vasculitis” (PCNSV) is restricted to the central nervous system. In contrast, secondary vasculitides may occur in the course of underlying systemic inflammation such as infections, neoplasias, drug abuse as well as connective tissue diseases and other systemic autoimmune disorders.

Table 2 Examples for the classification of primary vasculitides depending on the affected vessel size

	Large-sized vessels (ICA, A1, M1, P1, VA, BA)	Medium-sized vessels (M2, ACA, Pcom)	Small-sized vessels (arterioles, venules, capillaries)
Takayasu arteritis	X		
Giant cell (temporal) arteritis	X		
Polyarteritis nodosa		X	
Primary angiitis of the central nervous system	(X)	X	X
Wegener's granulomatosis			X
Vasculitis in connective tissue diseases			X
Behçet's disease			X
Vasculitis in connective tissue diseases (e.g. SLE)			X

Table 3 Imaging signs of cerebral vasculitides

	MRI	DSA
Vascular changes	T1-weighted: increased thickness of vessel wall	Abnormal straightening and/or kinking of arteries
	Postcontrast T1-weighted: mural enhancement	Multiple micro-aneurysms (rare, but highly specific)
	T2-weighted: vessel wall edema (may persist despite clinical remission)	Stenoses (one or multiple)
	Non-atherosclerotic arterial stenoses and occlusions	No prevalence of stenoses to vascular branching points
Parenchymal changes	Ischemic brain lesions (multiple infarcts of different ages; located in various vascular territories)	
	Intracerebral or subarachnoid hemorrhage	
	Cerebral perfusion deficits	
	Postcontrast T1-weighted: enhancement of leptomeningeal tissue adjacent to affected vessels	

Various inflammatory pathways induce endothelial cell activation. Subsequent changes of the intima may lead to accelerated atherosclerosis with occlusion, micro-aneurysms, and/or rupture of the respective vessel.

Since the caliber of the affected vessels may be indicative with regard to possible differential diagnoses, a classification of vasculitides according to the vessel size is helpful from the neuroradiological point of view. According to the traditional Chapel Hill nomenclature which was developed for systemic diseases, most intracranial vessels would fall into the category of either small- or medium-sized (Jennette et al. 1994); hence, this chapter categorizes intracranial vasculitides according to the vessel size as proposed by (Kueker 2007), whereby cerebral vessels with a diameter of more than 2 mm would be considered large (Table 2). They comprise the ICA, the M1 segment of the MCA, the A1 segment of the ACA, the P1 segment of the PCA, the intracranial VA, and the BA. Vasculitides that may target large vessels include giant cell (temporal)

arteritis, Takayasu's arteritis, PCNSV as well as virus and bacterial-associated vasculitides. In patients who present solely with large-vessel involvement, tissue biopsies are not feasible; hence, neuroimaging becomes an indispensable diagnostic tool. Direct signs of vessel wall changes may be detected by DSA, MRA, and MRI (Table 3; Kueker et al. 2008). Thickened vessel walls may be visualized by advanced MR sequences, which help to distinguish between noninflammatory and inflammatory (edema, contrast enhancement of vessel wall) origin (Giannini et al. 2012). Indirect signs of vasculitis as deduced from the pattern of parenchymal damage can be assessed by MRI.

Medium-vessel vasculitides affect cerebral arteries distal to the bifurcation of the MCA as well as the anterior and posterior communicating arteries (ACA and Pcom). The prevalence appears to be higher in older patients. The prototypical medium-vessel vasculitis is panarteritis nodosa (PAN). Furthermore, medium-sized vessels may be involved in systemic lupus erythematosus (SLE) and Behçet's disease.

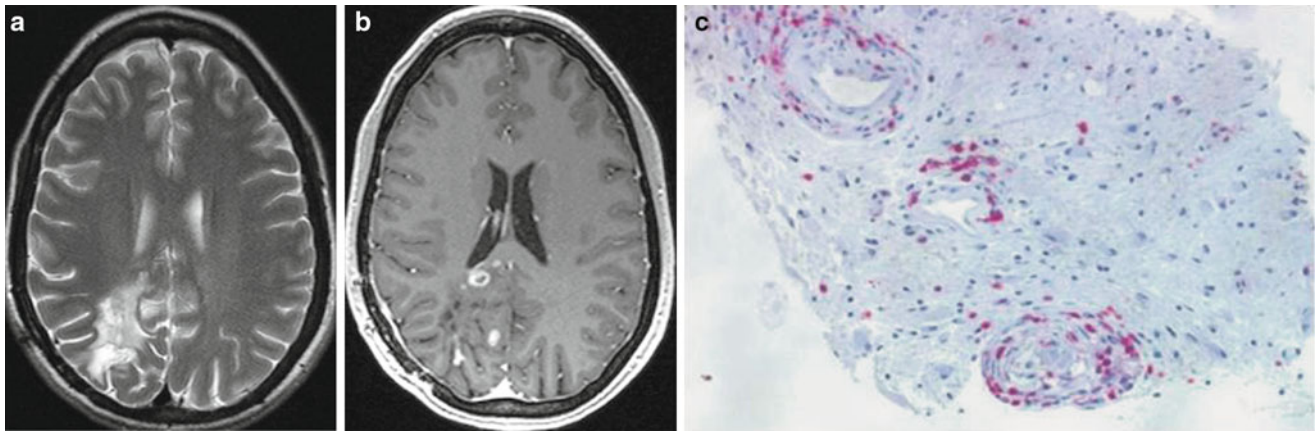


Fig. 1 Primary angiitis of the central nervous system (PACNS). A 27-year-old woman with headache and leg twitching. **a** Axial T2-weighted image. **b** Axial T1-weighted image after contrast administration. **c** Immunohistochemical preparation of stereotactic brain biopsy. Laminar hyperintensity of the right subcortical and

cortical parietooccipital region on T2-weighted images (**a**). Multifocal patchy and circular contrast enhancement at the border between gray and white matter (**b**). Fibrinoid necrosis and CD8+ lymphocytic infiltration of cerebral vessels, consistent with the diagnosis of vasculitis (**c**; courtesy of M.D. Siegelin, Neuropathology Heidelberg)

Small-vessel vasculitides affect arterioles, venules, as well as capillaries. This rare type of vasculitis includes Wegener's granulomatosis, microscopic polyangiitis, Sjögren syndrome, and cryoglobulinemic vasculitis; however, often enough vasculitic syndromes, such as Wegener's granulomatosis, do not adhere to vessel-size boundaries. The inflammatory changes of small cerebral vessels are beyond the spatial resolution of currently routinely available vascular imaging techniques and consequently require brain or leptomeningeal biopsy. Nevertheless, that diagnostic pathway may possibly change with the introduction of ultra high field strength MRI in the clinical routine application.

MRI has a high sensitivity for cerebral vasculitides, particularly with respect to secondary tissue damage, but a low specificity. There is no imaging sign pathognomonic for vasculitis and the appearance can be similar irrespective of the underlying disease mechanism; however, multiple infarcts in various vascular territories and of different ages are suggestive of cerebral vasculitis, in particular in young patients.

Due to the higher spatial resolution of DSA (approximately 100–200 μm), conventional angiography should corroborate the presumed diagnosis when lab studies and clinical presentation are highly suspicious and if MRI or MRA results are negative or ambiguous.

In some cases biopsy may still be required to render a definitive diagnosis. Albeit still considered the gold standard in the diagnosis of vasculitis, with a sensitivity of approximately 75 %, even histopathology may yield inconclusive or false-negative results due to sampling error; thus, negative histopathology results do not forcibly exclude the diagnosis of vasculitis.

Taken together, large-vessel vasculitides may be diagnosed by MRI, medium-vessel vasculitides often require additional angiography, and small-vessel vasculitides may

entirely evade detection by vascular imaging and therefore necessitate histological proof ("the smaller the affected vessel, the more invasive the required diagnostic procedure"). Despite the lack of specific signs, neuroimaging can be employed to assess the extent and type of lesions and to monitor the treatment response.

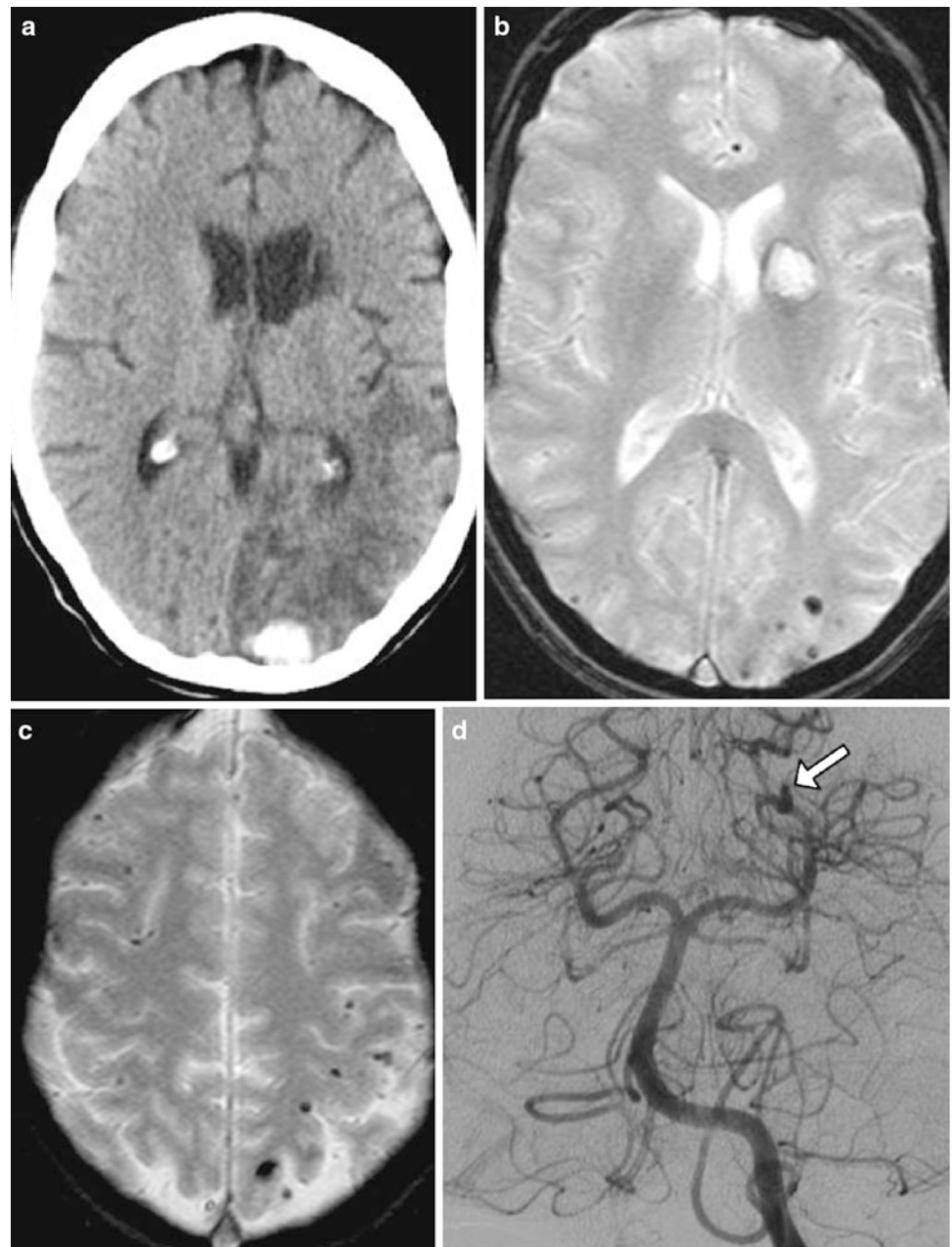
2.1.1 Primary Central Nervous System Vasculitis

Primary central nervous system vasculitis (PCNSV) is the most frequent vasculitis involving brain and spinal cord. Since it is limited to the nervous system it is being referred to as "primary angiitis of the CNS" (PACNS) or "primary central nervous system vasculitis" (PCNSV) (both terms are used synonymously).

Generally, patients of all age groups can be affected by this heterogeneous type of vasculitis, including children (cPCNSV or cPACNS = primary angiitis of the CNS in childhood). Most patients are between 40 and 60 years old at the time of diagnosis (Salvarani et al. 2007). In most cases the underlying pathophysiology is a noninfectious granulomatous angiitis affecting the nervous system; however, non-granulomatous histologies have been more and more reported recently (Giannini et al. 2012). Intracranial vessels of all sizes may be involved, predominantly leptomeningeal arteries and veins.

For clinicians and neuroradiologists alike, its diagnosis is challenging due to the absence of specific signs. Clinical symptoms include headache, non-focal and less frequently focal neurological signs. Imaging signs are typically multifocal caliber changes of the vessels; thus, multiple irregular-shaped stenoses or occlusions alternating with dilated segments. The most common MR imaging finding is multifocal infarctions in acute stages (in about 50 %), that typically involve the cortex and subcortical regions as well as deep

Fig. 2 Suspected primary angiitis of the central nervous system (PACNS). A 45-year-old woman with aphasia and right hemianopsia. Imaging signs are highly suggestive of cerebral vasculitis, despite negative CSF and histology results. Arguably, the posterior infarct might be a result of an embolus from an atrial myxoma which was found in this patient; however, this cannot sufficiently explain the multiple microaneurysms and petechial hemorrhages, which are typical findings in cerebral vasculitis. **a** Axial CT. **b, c** Axial T2*-weighted GRE image. **d** DSA of the left vertebral artery, frontal view. Old ischemic defect in the head of the left caudate nucleus, demarcated left posterior infarct and concomitant occipital parenchymal hemorrhage (**a**). Multifocal punctate areas of susceptibility low-signal intensity at the gray–white matter junction as a result of petechial hemorrhages, most prominently in the left parietal lobe (**b, c**). Classical appearance of vasculitis on DSA with multiple caliber changes including microaneurysms (**d**, arrow)



gray matter. Further MR signs include parenchymal and leptomeningeal enhancement, tumor-like masses, and signal-altered areas on FLAIR or T2-weighted images ((Birnbaum and Hellmann 2009, Zuccoli et al. 2011, Giannini et al. 2012). The SWI may present petechial hemorrhages with hemoglobin degradation products. MRA is relatively insensitive and may often be normal. (Figs. 1, 2).

2.1.2 Panarteritis Nodosa

Panarteritis Nodosa (PAN) is the most common systemic vasculitis that affects the CNS. The highest prevalence occurs in the fifth and sixth decades of life; young people

are usually not affected. Characteristically, fibrinoid necrosis of the internal and external elastic lamina leads to the destruction of the vessel wall and consequent formation of microaneurysms and/or luminal obliteration (Fig. 3).

2.1.3 Giant Cell (Temporal) Arteritis

Giant cell arteritis results from granulomatous vessel wall infiltration of large arteries. Mainly the temporal arteries are affected (hence, the name), although occipital or other arteries may be involved additionally or alternatively. Temporal arteritis may be diagnosed by Doppler ultrasonography, which can depict both the vessel lumen and the vessel wall.

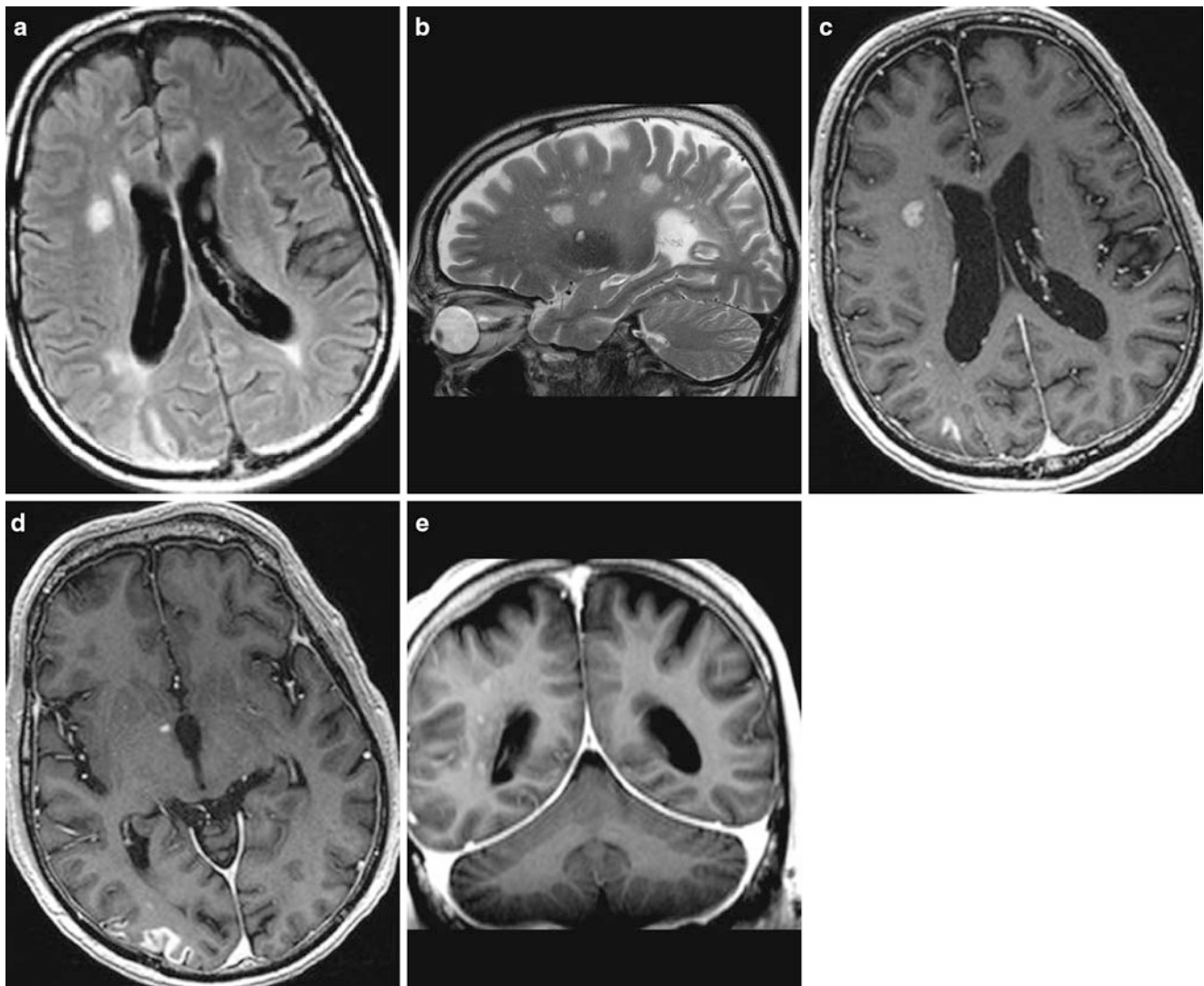


Fig. 3 Panarteritis nodosa (PAN). A 65-year-old man with loss of vigilance and intermittent hemiparesis of the left side. Biopsy of the cerebellum and meninges yielded pathological features compatible with those of cerebral vasculitis. He died 3 months after hospital admission. **a** Axial FLAIR image. **b** Sagittal T2-weighted image. **c**, **d** Axial T1-weighted images after contrast administration. **e** Coronal T1-weighted image after contrast administration. Irregular subcortical and cortical signal changes of the right hemisphere (**a**). Patchy hyperintense areas on T2-weighted images in the right cerebral hemisphere (**b**). Multiple right-hemispheric contrast-enhancing lesions, patchy in the periventricular white matter and garland-like in the cortex of the right occipital cortex (**c**, **d**). Punctate nodular

contrast enhancement in the white matter of the right hemisphere (**e**). **e** Panarteritis nodosa (PAN). A 65-year-old man with loss of vigilance and intermittent hemiparesis of the left side. Biopsy of the cerebellum and meninges yielded pathological features compatible with those of cerebral vasculitis. He died 3 months after hospital admission. **e** Coronal T1-weighted image after contrast administration. Irregular subcortical and cortical signal changes of the right hemisphere (**a**). Patchy hyperintense areas on T2-weighted images in the right cerebral hemisphere (**b**). Multiple right-hemispheric contrast-enhancing lesions, patchy in the periventricular white matter and garland-like in the cortex of the right occipital cortex (**c**, **d**). Punctate nodular contrast enhancement in the white matter of the right hemisphere (**e**)

The vessel wall edema may be visualized by ultrasound as a characteristic and highly sensitive concentric hypoechogenic mural thickening (“halo sign”). Several studies have reported high sensitivity of MRI in giant cell arteritis (Bley et al. 2005). In particular, vessel wall changes, which are mural thickening and contrast enhancement of the temporal arteries and other large vessels, are sensitive signs. The higher the employed field strength of the MR scanner, the better is the

sensitivity for vessel wall changes in MRI and MRA (Fig. 4; Pipitone et al. 2008).

2.1.4 Takayasu’s Arteritis

Takayasu’s arteritis (“pulseless disease”) represents an idiopathic granulomatous giant cell arteritis, primarily affecting the aorta and its major branches. Characteristically marked thickening of the affected vessels with long, smooth

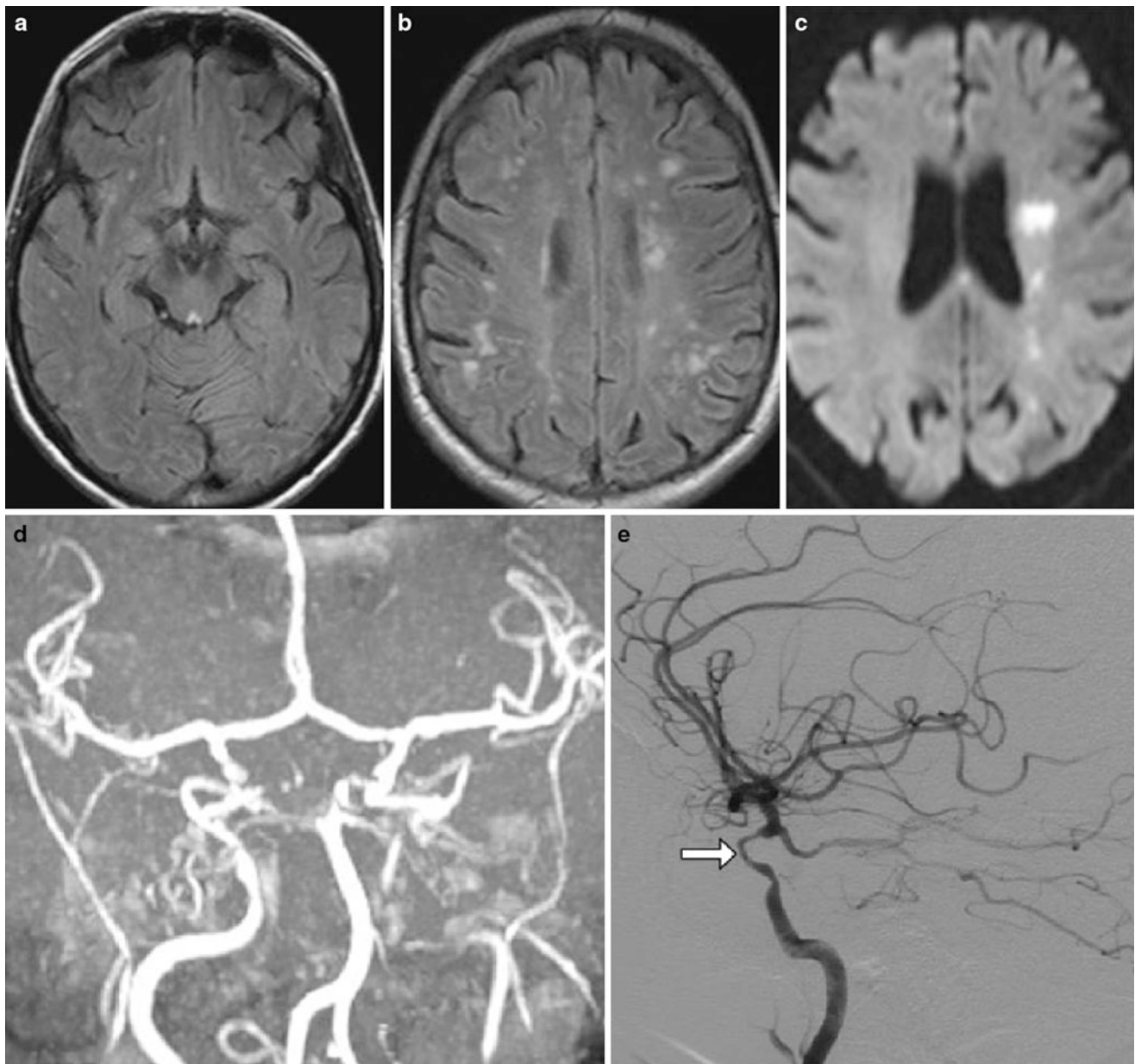


Fig. 4 Giant cell (temporal) arteritis. A 61-year-old woman presenting with hemiparesis of the right side and psychosis. The psychotic symptoms disappeared subsequent to the administration of high-dose steroids. **a, b** Axial FLAIR images. **c** Axial DWI. **d, e** Giant cell (temporal) arteritis. A 61-year-old woman presenting with hemiparesis of the right side and psychosis. The psychotic symptoms disappeared subsequent to the administration of high-dose steroids.

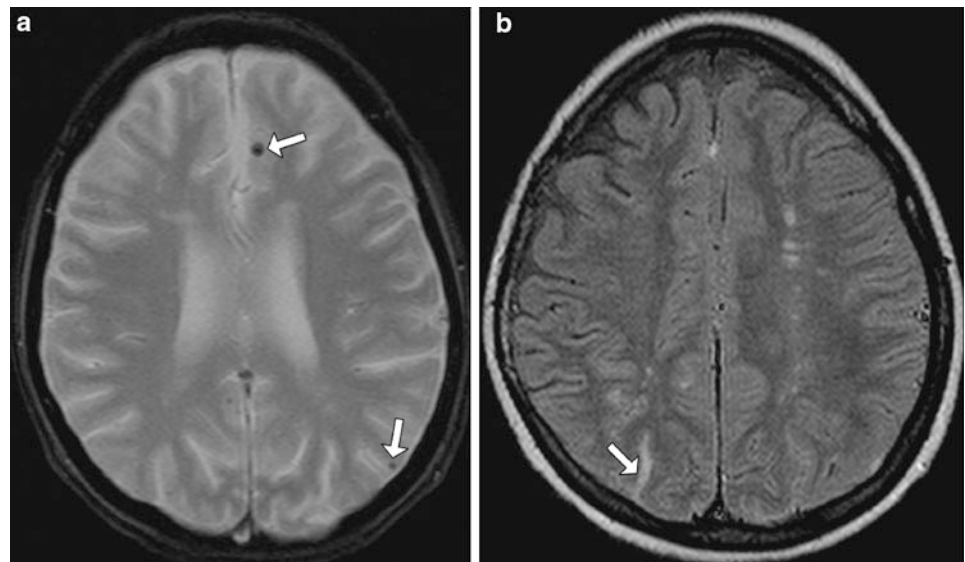
d MIP of an arterial TOF MRA. **e** DSA of the right ICA, lateral view. Multifocal patchy signal changes in the subcortical and deep white matter of both hemispheres (**a, b**). Acute ischemic border zone infarction in the left corona radiata (**c**). Irregular and partially absent flow in the left ICA (**d**) and high-grade stenosis of the ophthalmic segment of the right ICA (**e**, arrow)

stenoses, and sometimes occlusions, becomes visible on DSA and MRA (Pipitone et al. 2008). Since large vessels are affected, vessel wall edema may be visualized using MR imaging. Diffuse dilations and aneurysms are not uncommon (Kelley 2004).

2.1.5 Wegener's Granulomatosis

This chronic systemic arteritis involves lungs, kidneys, and paranasal sinuses. The CNS is affected in less than 10 % of patients. In such cases, intracerebral and meningeal necrotizing granulomas or vasculitis may occur.

Fig. 5 Systemic lupus erythematosus (SLE) in a 21-year-old woman with renal and cerebral affection. **a** Axial T2* GRE-weighted image. **b** Axial FLAIR image. Petechial hemorrhages in the frontal and parietal cerebral cortex (**a**, arrows). Multifocal patchy white matter hyperintensities in the centrum semiovale as well as subarachnoid parietal hemorrhage (**b**, arrows)



Wegener's-associated vasculitis can lead to arterial or venous thrombosis as well as hemorrhage (Kelley 2004). Since the caliber of the affected vessels (50–300 μm in diameter) may be beyond the spatial resolution of DSA, and lesions of the brain parenchyma itself are rare, radiologically confirmed CNS vasculitis in Wegener's granulomatosis is exceptional; however, involvement of the dura with pachymeningitis may be detected on MR imaging after contrast administration (Chin and Latov 2005).

2.1.6 Systemic Lupus Erythematosus

Systemic lupus erythematosus is a chronic inflammatory connective tissue disorder that affects many organ systems. The CNS is involved in up to 75 % of cases and patients may present with a wide range of neurological and psychiatric manifestations (neuropsychiatric SLE). Cerebral SLE lesions occur as focal or multiple T2 hyperintensities, either as infarctions or as a correlate of symptomatic "migratory" edematous areas. Accordingly, water diffusion may be either restricted in early stages of ischemia (cytotoxic edema) or increased in vasculopathy (vasogenic edema).

The most common imaging findings in SLE are cortical atrophy, ventricular dilation, and fronto-parietal rounded or patchy lesions, which are not limited to the periventricular white matter. In fact, they can be localized in the gray–white junction, the cortex, or the basal ganglia. Contrast enhancement may be attributed to leakage in active lesions.

Venous MRA may show dural venous sinus thrombosis and should be performed particularly in antiphospholipid syndrome. Increased choline in proton MRS correlates with disease activity.

FDG-PET may be a useful tool in neuropsychiatric SLE if standard MRI appears to be normal: Active SLE with

cerebral affection is correlated with decreased metabolism in parieto-occipital regions (Figs. 5, 6).

2.1.7 Scleroderma

In progressive systemic sclerosis, excessive collagen deposition in the skin, blood vessels, and other organs leads to abnormal tissue fibrosis and microvascular impairment. CNS manifestations are extremely rare (Fig. 7).

2.1.8 Sjögren Syndrome

Approximately 20 % of patients with Sjögren syndrome present with neurological symptoms. The cerebral vasculitis resembles PAN with vessel stenoses and dilations. Enlarged ventricles due to white matter volume loss have been repeatedly reported (Fig. 8; Di Comite et al. 2005).

2.1.9 Behçet's Disease

Only 5 % of Behçet patients present with CNS involvement. In such cases, MRI depicts scattered subcortical white matter lesions which may show contrast enhancement in the acute phase. Characteristically, the lesions are preferentially located in the midbrain, whereas the cortex is usually spared (Fig. 9).

2.1.10 Viral Vasculitis

Varicella zoster virus is a frequent cause of cerebral vasculitis affecting mainly large cerebral vessels. Often the intracranial carotid bifurcation and the M1 segment of the MCA, but also the BA, are targeted. The clinical and neuroradiological characteristics of proven zoster vasculopathy and PACNS are so similar, that it may be speculated whether in a subgroup of PACNS the underlying cause is an undiagnosed zoster infection (Kueker 2007).

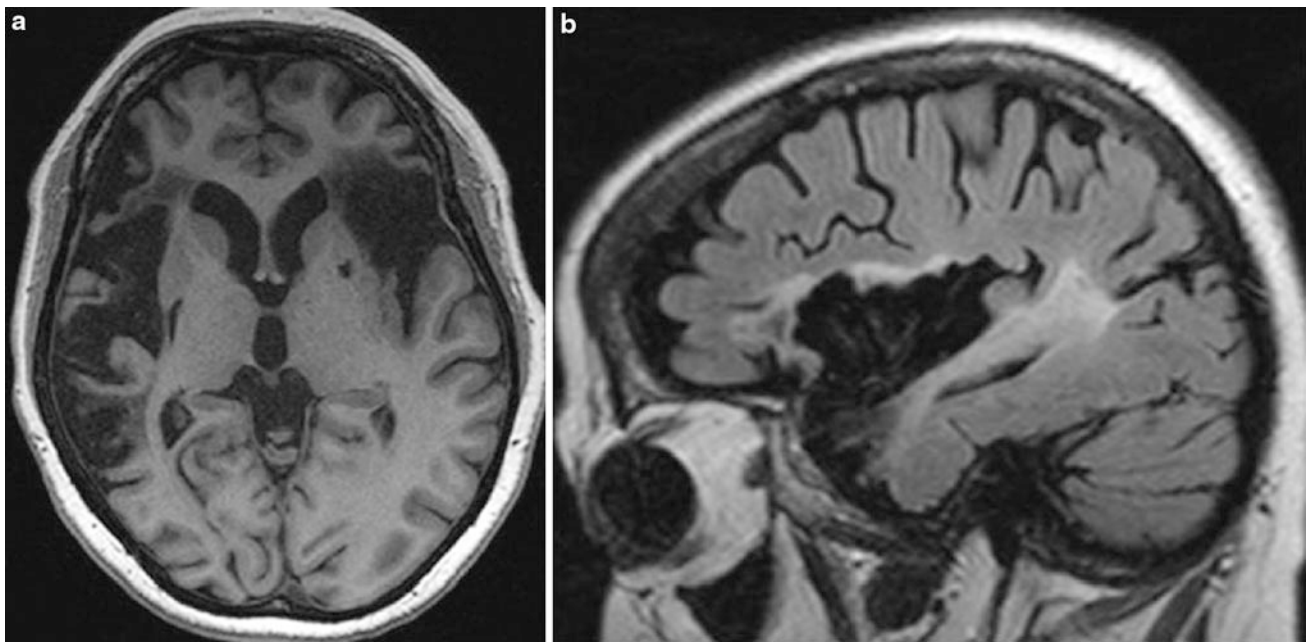


Fig. 6 Systemic lupus erythematosus (SLE). This 46-year-old woman has been diagnosed with SLE 26 years ago and has been suffering from cerebral affection for 24 years. **a** Axial T1-weighted image. **b** Sagittal FLAIR image. Chronic bilateral ischemic infarcts in the

territory of the MCA (**a**) with reactive gliosis (perifocal hyperintensity on FLAIR images) (**b**). Note the enlarged ventricles as a result of white matter reduction

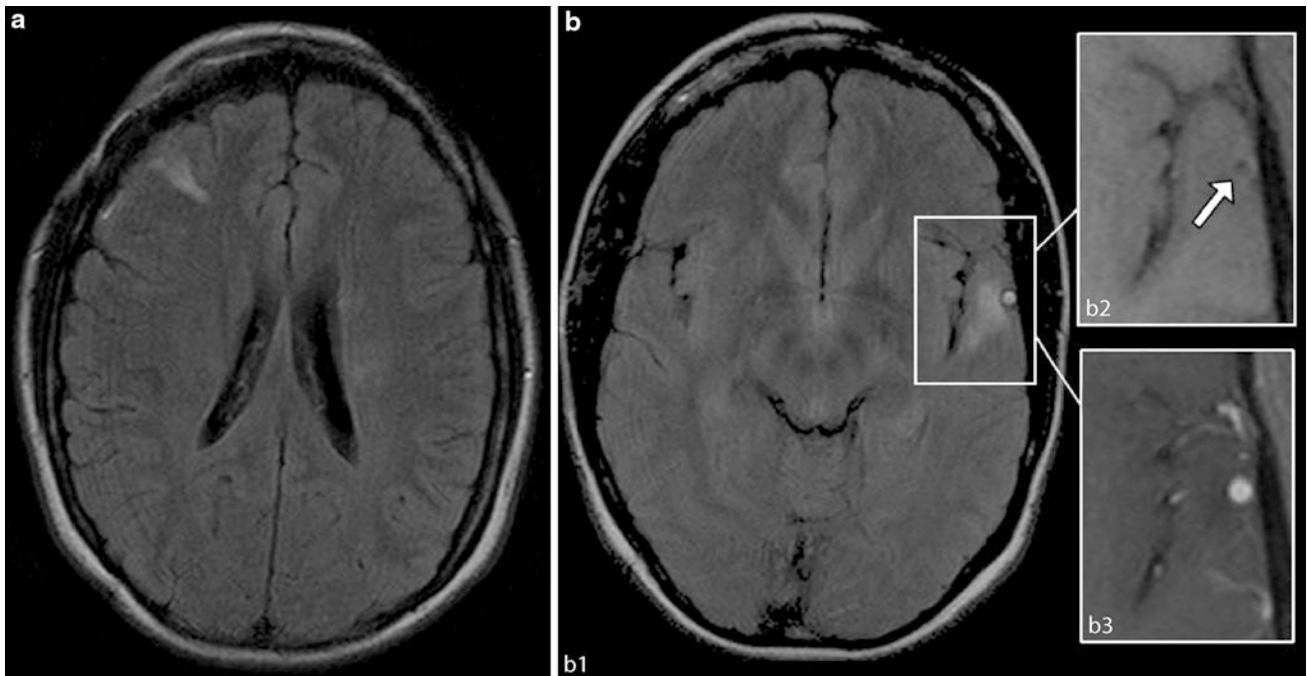


Fig. 7 Cerebral arteriopathy in scleroderma. A 32-year-old woman with linear scleroderma “en coup de sabre.” Focal epilepsy starting five years ago was the first sign of cerebral affection. **a** Axial FLAIR-weighted image. **b** Axial FLAIR-weighted images (**b1**). Detail images of axial T1-weighted images of the left anterior temporal pole before (**b2**) and after contrast administration (**b3**). Right frontal (**a**) and left temporopolar (**b1**) cortical and subcortical white matter hyperintensities.

Microaneurysm of a leptomeningeal vessel (**b1–b3**) with hyperintensity of the inner layer of the vessel wall on FLAIR image reflecting the intimal edema (**b1**). The vessel wall is thickened and therefore visible as a slightly hyperintense structure on non-enhanced T1-weighted images (**b2**, arrow). After gadolinium administration, all layers of the vessel wall exhibit severe contrast enhancement (**b3**)

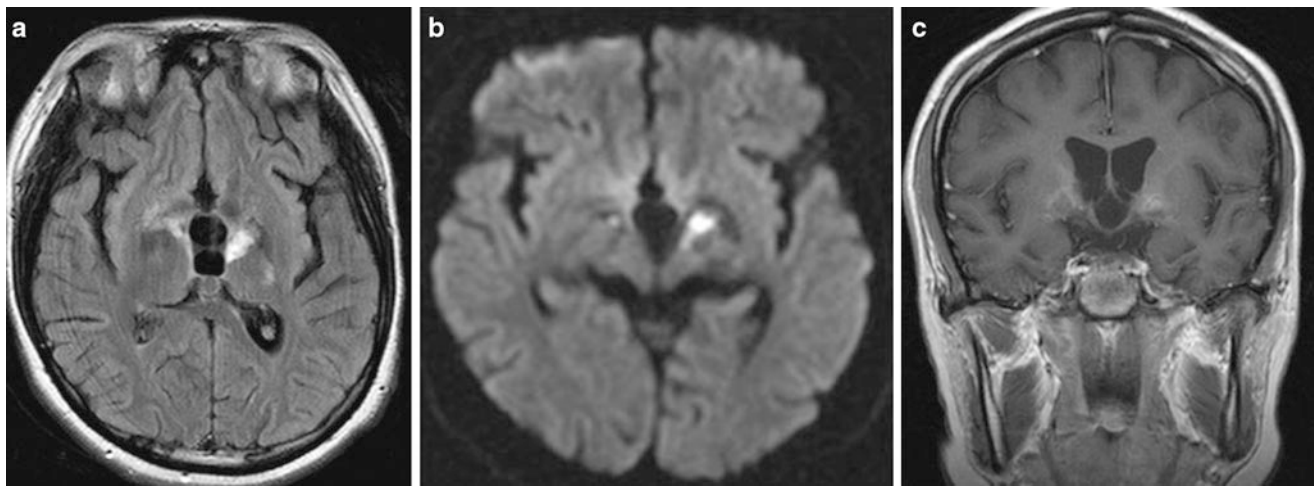
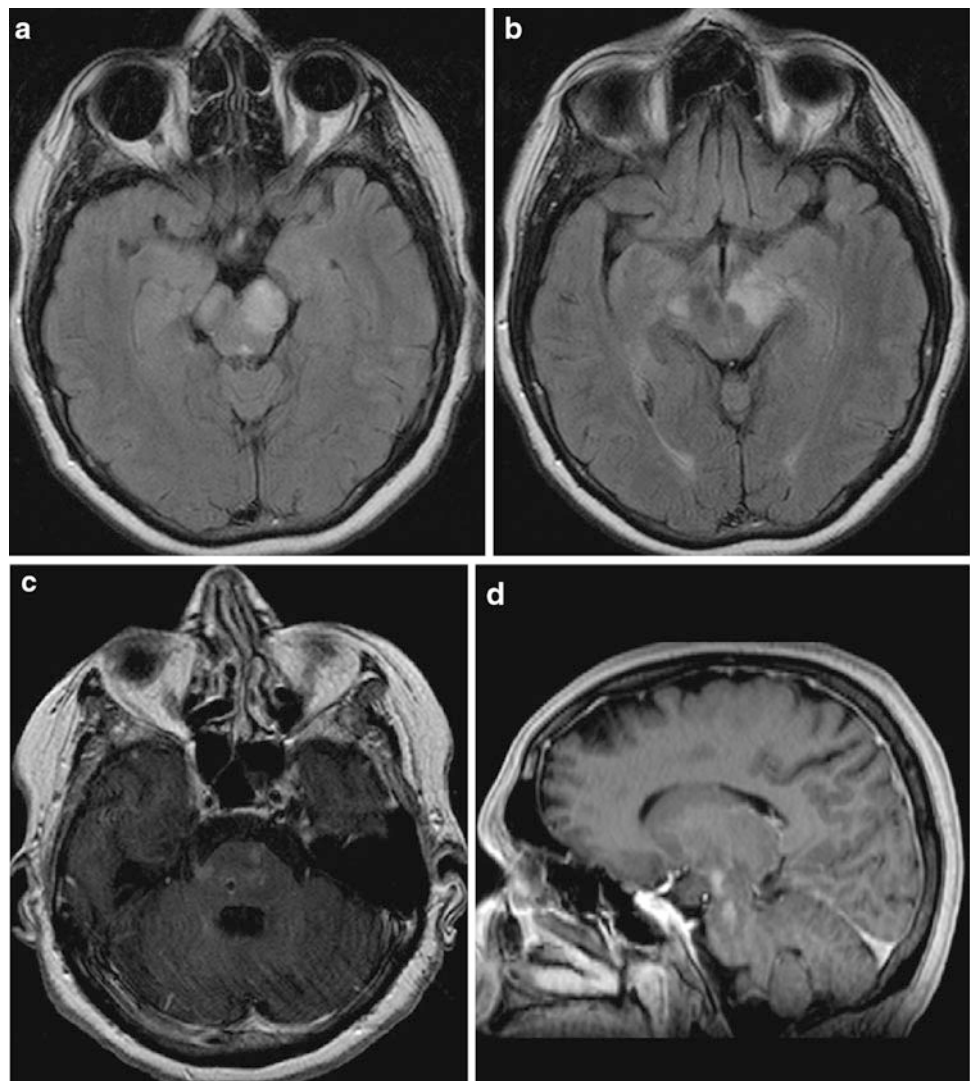


Fig. 8 A 20-year-old woman with Sjögren syndrome and associated CNS vasculitis. Since the age of 16 she has been suffering from sicca symptoms and hypothalamic dysfunction, the latter resulting in narcolepsy as well as postural and gait instability. **a** Axial FLAIR image. **b** Axial DWI. **c** Coronal T1-weighted MR image after contrast administration. Bilateral hyperintensities of the basal ganglia, predominantly of the left

thalamus (**a**). Restricted diffusion in the left thalamus (**b**). Hemorrhagic transformation of bilateral thalamic infarctions with high signal on T1-weighted MR image (**c**). The basal ganglia hyperintensities were visible prior to contrast application as well (not shown). Note the enlarged ventricles due to loss of adjacent white matter

Fig. 9 Behçet's disease. A 56-year-old woman with dysarthria and labile affect due to brain-stem encephalitis associated with neuro-Behçet syndrome. **a, b** Axial FLAIR images. **c** Axial T1-weighted image after contrast administration. **d** Sagittal T1-weighted image after contrast administration. Marked swelling and signal changes of the pons and cerebral peduncles (**a, b**). Lacunar pontine lesion (**c**) and abnormal contrast enhancement of the pons and mesencephalon (**c, d**)



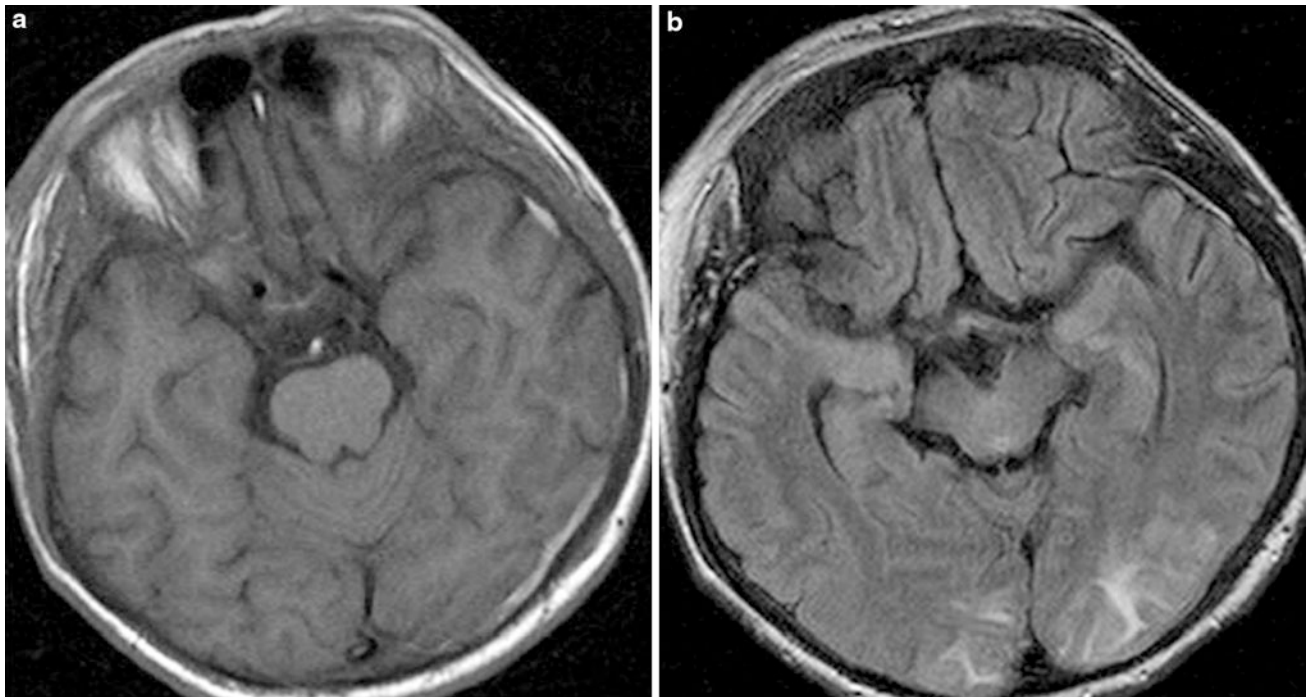


Fig. 10 Viral vasculitis (*Varicella zoster*). A 37-year-old immuno-compromised man with ophthalmic zoster presenting with alternating phases of reduced vigilance and severe agitation. In the CSF *Varicella* viruses were found (as confirmed by PCR). **a** Axial T1-weighted image. **b** Axial FLAIR image. Left temporal acute, T1-hyperintense

Other DNA viruses from the herpes family, such as herpes simplex virus type 1 and cytomegalovirus, may cause large-vessel vasculitis as well. Furthermore, RNA viruses, such as HIV, may be implicated. Indeed, the number of diagnosed HIV-associated vasculitides is increasing, especially in infants. The inflammatory response is particularly severe in AIDS patients (Fig 10; see also “[Viral Encephalitis](#)”).

2.1.11 Bacterial Meningitis

A number of bacterial agents may cause acute septic meningitis and cerebral vasculitis. Firstly, purulent infection at the base of the brain may lead to inflammatory cell infiltration of vessel walls. Additionally, vessel wall damage may be aggravated by the activated immune response (such as cellular adhesion molecules, complement, reactive oxygen species, and proteolytic enzymes). Late complications might be septic thrombosis and thrombophlebitis (Younger 2004).

In tuberculosis, inflammation of the adventitia of small- and medium-sized arteries triggers proliferation of reactive subendothelial cells. This in turn, leads to stenosis of the vascular lumina; therefore, MRA and DSA demonstrate narrowing of the basal cerebral or cortical vessels. Typically, vessels at the skull base are most commonly involved, often leading to hemorrhages (Fig. 11; see “[Neurotuberculosis](#)”).

SDH. The traumatic SDH was acquired during an agitation phase in which the patient fell off the bed (**a**). Bioccipital hyperintense subcortical lesions resembling posterior reversible encephalopathy syndrome (PRES; **b**)

2.1.12 Spirochetal Vasculitis

Treponema pallidum-associated cerebral vasculitis is caused by spirochetal invasion of the endothelial cells in the tertiary parenchymal syphilis syndrome. Diffuse vasculitis involves preferably cortical arteries and veins, whereas the gummatous vasculitis usually affects proximal MCA branches (see also “[Neurosyphilis](#)”).

Borrelia burgdorferi-associated cerebral vasculitis is believed to result from focal mononuclear inflammatory cell infiltration of blood vessels. The endothelial cell swelling may lead to stroke-like lesions as well as subarachnoid hemorrhage (Fig. 12; Younger 2004).

2.1.13 Drug-Induced Vasculitis

Currently it is well established that chronic drug abuse can damage vessels directly or indirectly (hypersensitivity to contaminants) and may therefore be associated with necrotizing arteritis. The severity of drug-induced cerebral vasculitis is influenced by the duration and degree of exposure, route of administration, immune status and, of course, the type of drug. In particular, drugs with sympathomimetic amine-type activity (amphetamines, cocaine, heroin etc.) have been repeatedly reported to induce cerebral vasculitis (Fig. 13).

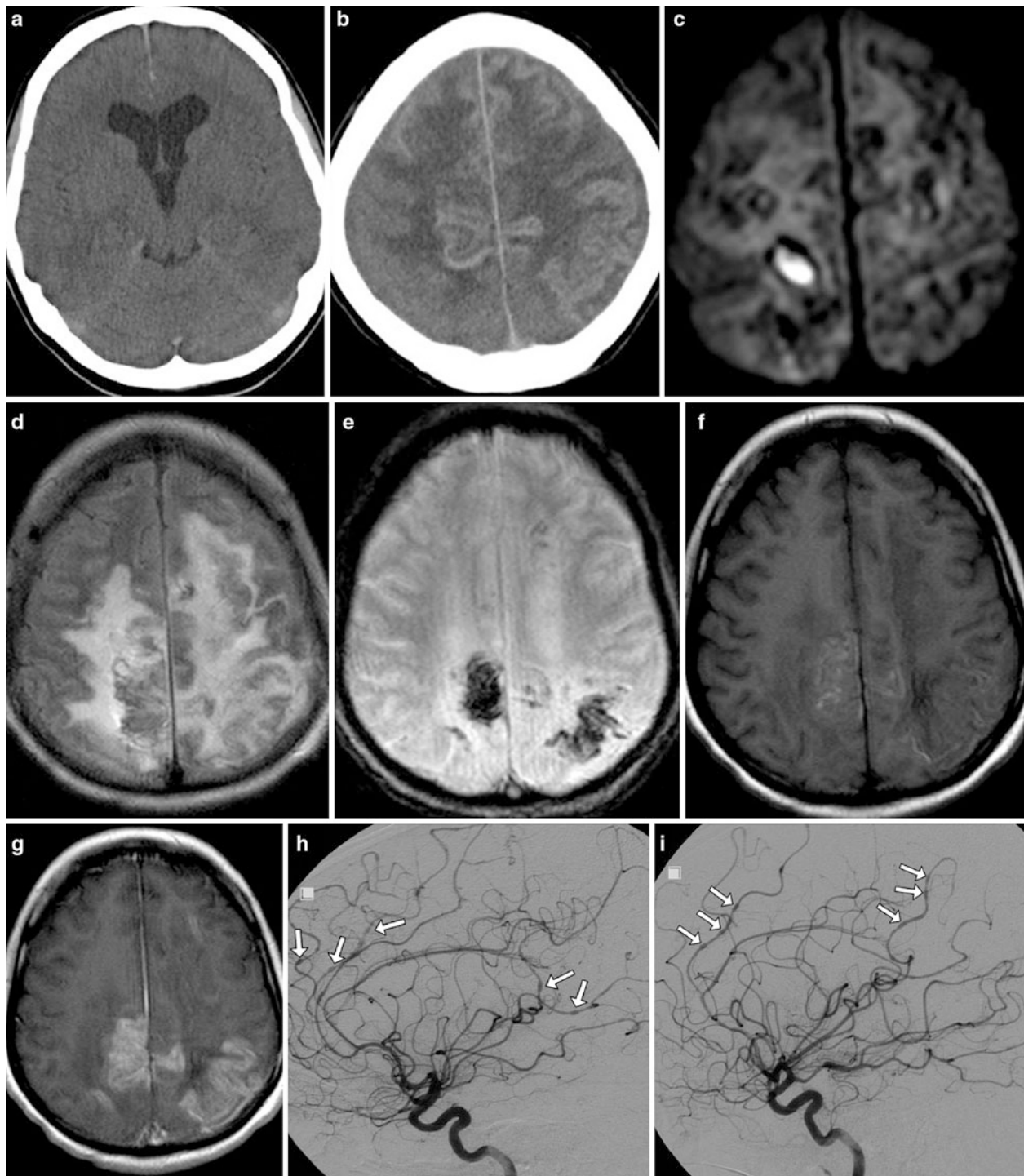
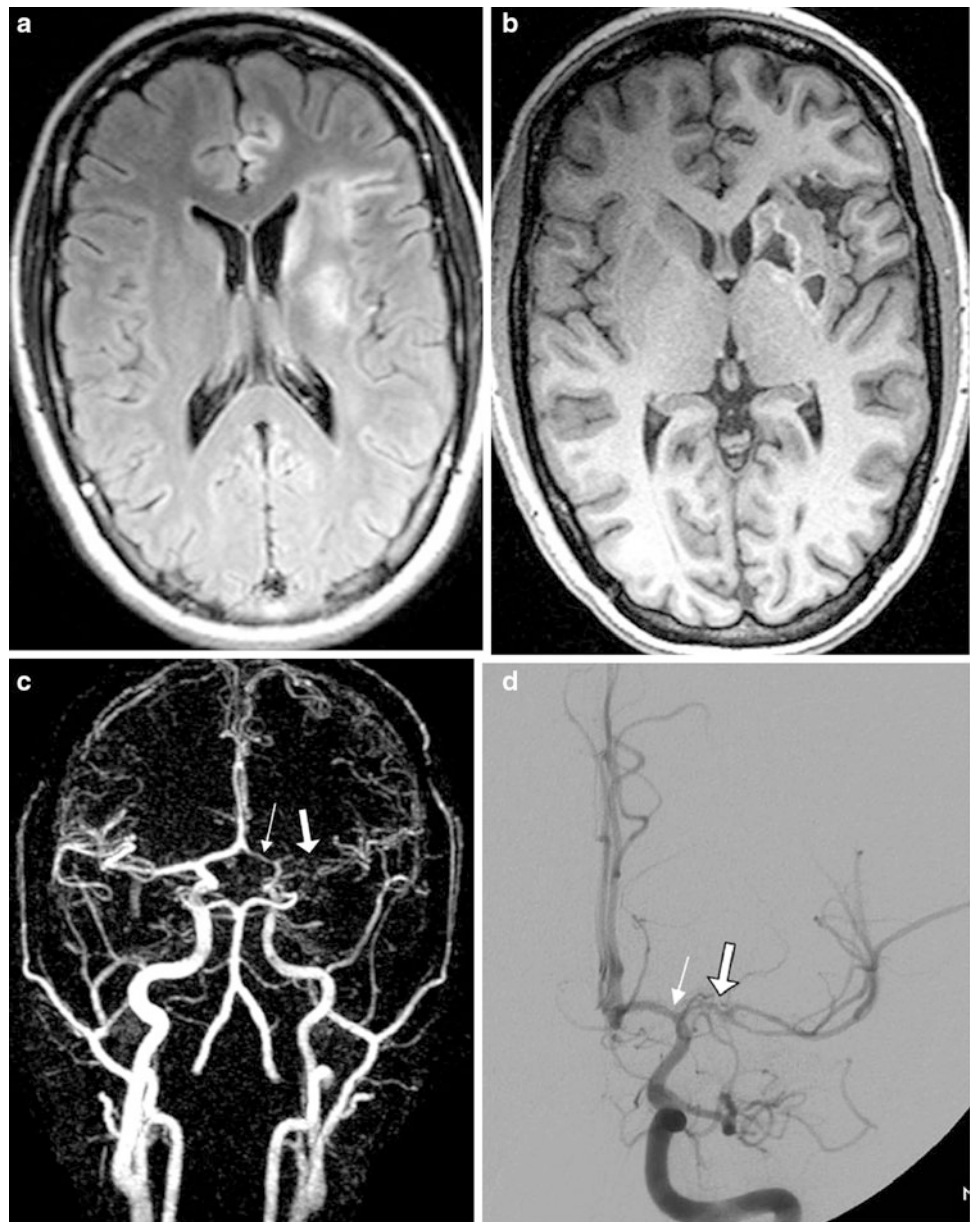


Fig. 11 Bacterial meningitis (*Mycobacterium tuberculosis*). A 40-year-old woman with tuberculosis for 15 years. She presented with acute pneumonia and reduced vigilance. **a, b** Axial CT. **c** Axial DWI. **d** Axial FLAIR image. **e–i** Bacterial meningitis (*Mycobacterium tuberculosis*). A 40-year-old woman with tuberculosis for 15 years. She presented with acute pneumonia and reduced vigilance. **e** Axial T2*-weighted image. **f** Axial T1-weighted image before contrast administration. **g** Axial T1-weighted image after contrast administration. **h, i** Bacterial meningitis (*Mycobacterium tuberculosis*). A 40-year-old woman with tuberculosis for 15 years. She presented with acute pneumonia and reduced vigilance. **h, i** DSA of the left ICA, lateral view. Initial CT demonstrated hydrocephalus (**a**) as well as cortical

hyperdensities and white matter hypodensities (**b**). MR imaging revealed infarctions and hemorrhages (**c–g**). Focal area of restricted water diffusion in the subcortical white matter of the left hemisphere (**c**). Extensive laminar hyperintensities of bilateral gray and white matter (**d**) demonstrate severe parenchymal edema. Several large areas of signal loss on SWI due to hemoglobin degradation products (**e**). The cortex shows moderate hyperintensity (**f**) due to hemorrhagic transformation. Severe irregular cortical, subcortical, and even meningeal contrast enhancement (**g**). Alternating areas of vessel constriction and dilation of the anterior and middle cerebral artery, exhibiting “sausage-string” appearance (**h, i**, arrows: microaneurysms)

Fig. 12 Spirochetal vasculitis (*Borrelia burgdorferi*). A 20-year-old woman with erythema migrans, bilateral headaches, and recurring cramps in the right hand. **a** Axial FLAIR image. **b** Axial T1-weighted image. **c** MIP of a arterial TOF MRA. **d** DSA of the left ICA, frontal view. Left-hemispheric hyperintensities mainly affecting cortical and subcortical gray matter in the territory of the left anterior and medial cerebral arteries (**a**). Marked defect of the left lentiform nucleus with surrounding mild hemorrhages and focal brain atrophy (**b**). Distinct tapering of the left A1 segment (**c**, **d**, *thin arrows*) and severe stenosis of the proximal left MCA (**c**, **d**, *thick arrows*) with rarefaction in the periphery (**c**, **d**)



2.2 Differential Diagnoses of Cerebral Vasculitides

2.2.1 Intracranial Atherosclerotic Vascular Disease

In adults atherosclerosis is by far the most common cause of a vasculitis-mimicking angiographic pattern. ASVD affects mainly patients of advanced age and usually coincides with atherosclerosis of extracranial arteries such as coronaries. Atherosclerotic plaques preferentially affect the branching points of large vessels (which is unusual for vasculitis). In contrast, vasculitides usually involve smaller branches, and are more likely associated with haemorrhage.

2.2.2 Reversible Cerebral Vasoconstriction Syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is a rare disease, that can be easily mistaken for PCNSV. It presents with acute, very severe headaches ('thunderclap'), which may be recurrent over 1–3 weeks and might be associated with focal deficits and/or seizures. Although RCVS may occur spontaneously, in more than 50 % it follows "intracranial stress" such as exposure to vasoactive drugs (e.g. cocaine, amphetamine) or birth giving ("post-partum angiopathy") (Ducros et al. 2010).

Segmental multifocal arterial constriction and dilation leads to the characteristic "string of beads" or "sausage on

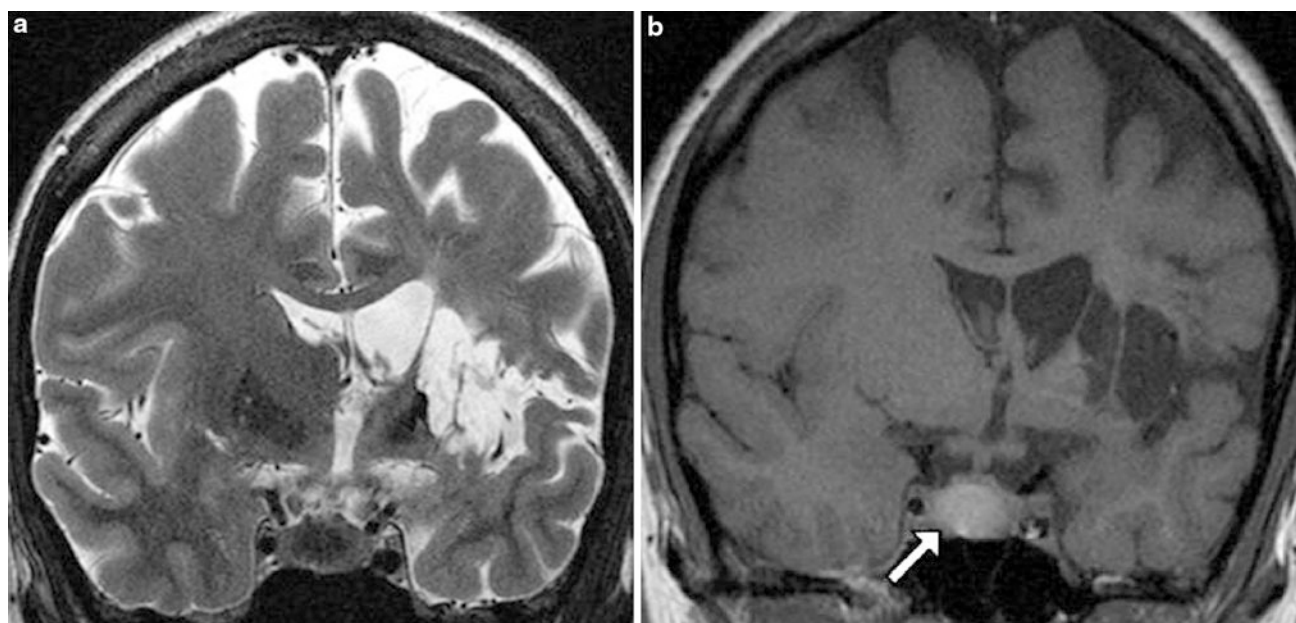


Fig. 13 Drug-induced vasculitis. A 22-year-old woman with chronic cocaine abuse. **a** Coronal T2-weighted image. **b** Coronal T1-weighted image. Parenchymal defects of the left basal ganglia and evacuation enlargement of the ipsilateral ventricles subsequent to an infarct in the

territory of the left MCA (**a, b**). Additionally, the pituitary gland is enlarged and demonstrates T2-hypointense (**a**) and T1-hyperintense signal changes (**b**) representing hemorrhage into the pituitary gland (*arrow*) possibly caused by vasculitis-associated hemorrhage

Table 4 Differentiation between primary CNS vasculitis (PCNSV) and Reversible Cerebral Vasoconstriction Syndrome (RCVS) [According to criteria reported by Sattar et al. (2010), Salvarani et al. (2012) and Giannini et al. (2012)]

	PCNSV	RCVS
Onset	Usually gradual and progressive	Acute, rapid development of symptoms Often precipitated in the postpartum or following exposure to vasoactive drugs
Course	Progressive with frequent appearance of cerebral infarcts	Monophasic Self-limited within 1–3 months
Commonest symptoms	Subacute and progressive headache, Altered cognition, Persistent neurologic deficit or stroke	“Thunderclap” headache (acute and severe)
Gender	Women are slightly more often affected than men	Women are more frequently affected than men (3:1)
CSF	Abnormal in 80–90 % of cases (white cell count and total protein concentration mildly increased)	Usually normal
MRI	Pathological in almost 100 %	Often normal during the first week MR angiography reveals diffuse segmental arterial constriction in up to 90 % after 1–2 weeks

a string” aspect on angiography. Since the initial vascular imaging may be normal in up to 90 %, a follow-up study 1–2 weeks after onset is usually required to demonstrate the characteristic segmental arterial constrictions. In the first week after onset, RCVS may be complicated by subarachnoid or intracerebral hemorrhage. In the second week,

(additional) ischemic lesions may occur, typically in the arterial border zone regions (Sattar et al. 2010).

Distinguishing RCVS from PANCS is often a dilemma. In order to prevent RCVS patients from receiving cytotoxic medication, the following criteria may be helpful to differentiate these two disease entities (see Table 4).

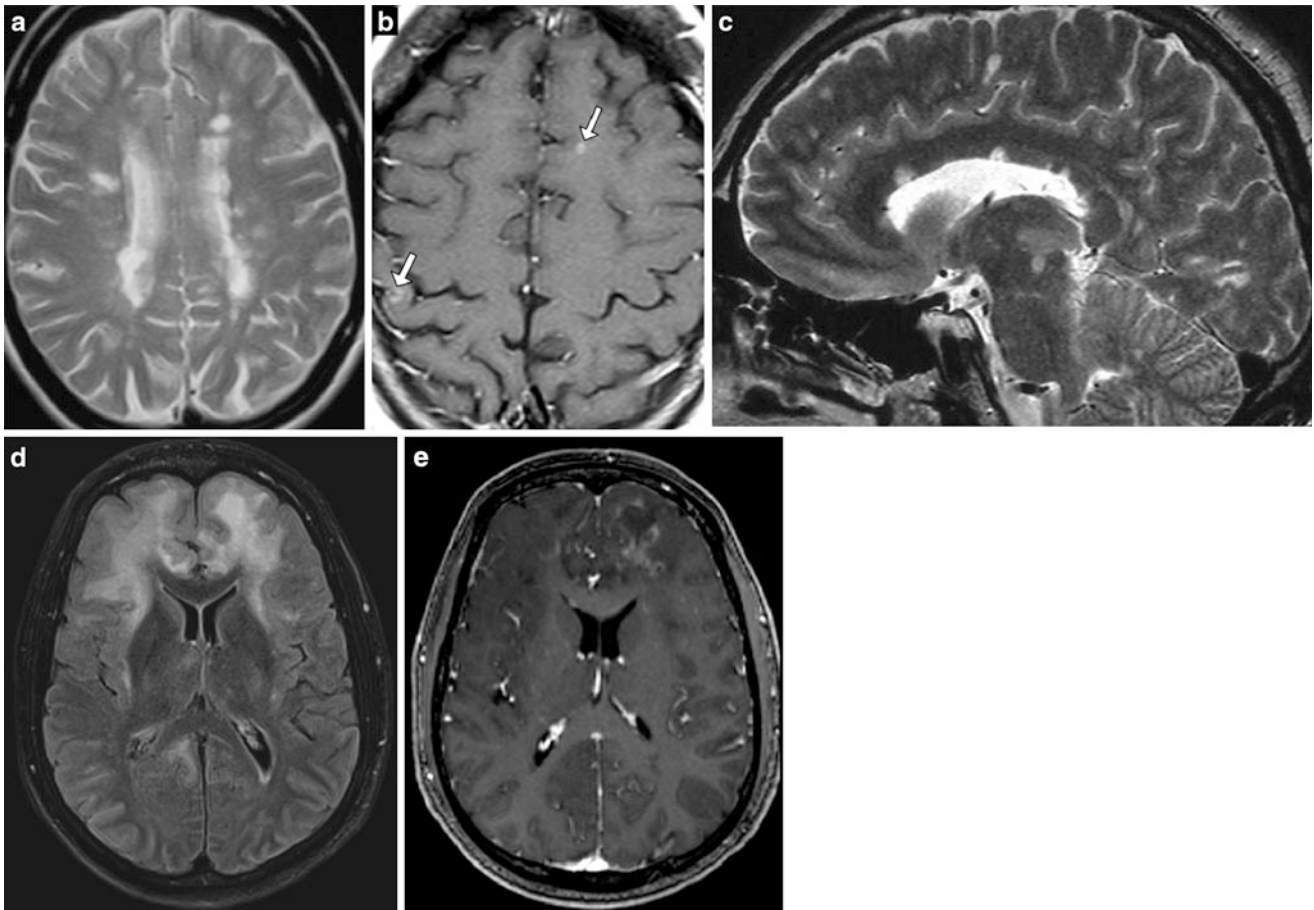


Fig. 14 Multiple sclerosis. **a** Axial T2-weighted image shows multiple bilateral periventricular round or ovoid hyperintensities. **b** Axial T1-weighted image after contrast administration depicts nodular enhancement as a correlate of active demyelination (arrows). **c** Multiple sclerosis. **c** The sagittal T2-weighted image through the midline demonstrates infra- and supratentorial MS plaques and the preferred

affection of the corpus callosum. **d, e** PML in a patient with Multiple sclerosis under the treatment with natalizumab. **d** Axial FLAIR image. **e** Axial T1-weighted image after contrast administration. Bifrontal and right occipital slightly space occupying hyperintensities on the FLAIR images with involvement of the subcortical U-fibres. In contrast to classical PML the lesions reveal contrast enhancement

2.2.3 Multiple Sclerosis

Typical MS plaques appear as multiple round or ovoid T2-hyperintensities with temporal and spatial dissemination. Most lesions are located in the periventricular white matter. Pathognomonic for MS lesions is their perpendicular orientation at the calloseptal interface along penetrating venules (“Dawson fingers”). Transient contrast enhancement indicates acute breakdown of the blood–brain barrier as a correlate of active demyelisation. In vasculitis, however, lesions are usually less numerous and there is no preferred affection of the corpus callosum. Instead, gray matter is more often involved in vasculitis (Fig. 14; see [Multiple Sclerosis](#)).

A rare but important complication of the treatment with monoclonal antibodies is the development of atypical progressive multifocal leukoencephalopathy (PML), which

might be difficult to differentiate from tumefactive MS (see “[Viral Encephalitis](#)”; Fig. 4).

2.2.4 Moyamoya Disease

Moyamoya disease is an angiographic pattern rather than a specific disease. It affects infants or young adults and is a frequent cause of stroke in Japanese children (idiopathic progressive arteriopathy of childhood). Probably triggered by various inflammatory causes, slow progressive (often bilateral) stenoses of the supraclinoid ICAs and later the BA lead to formation of abnormal lenticulostriate and thalamostriate collaterals which can be visualized on angiography as a cloudy net referred to as the “puff of smoke” sign (Japanese: “moyamoya”). The bright sulci on FLAIR and postcontrast T1-weighted MR images (leptomeningeal “ivy

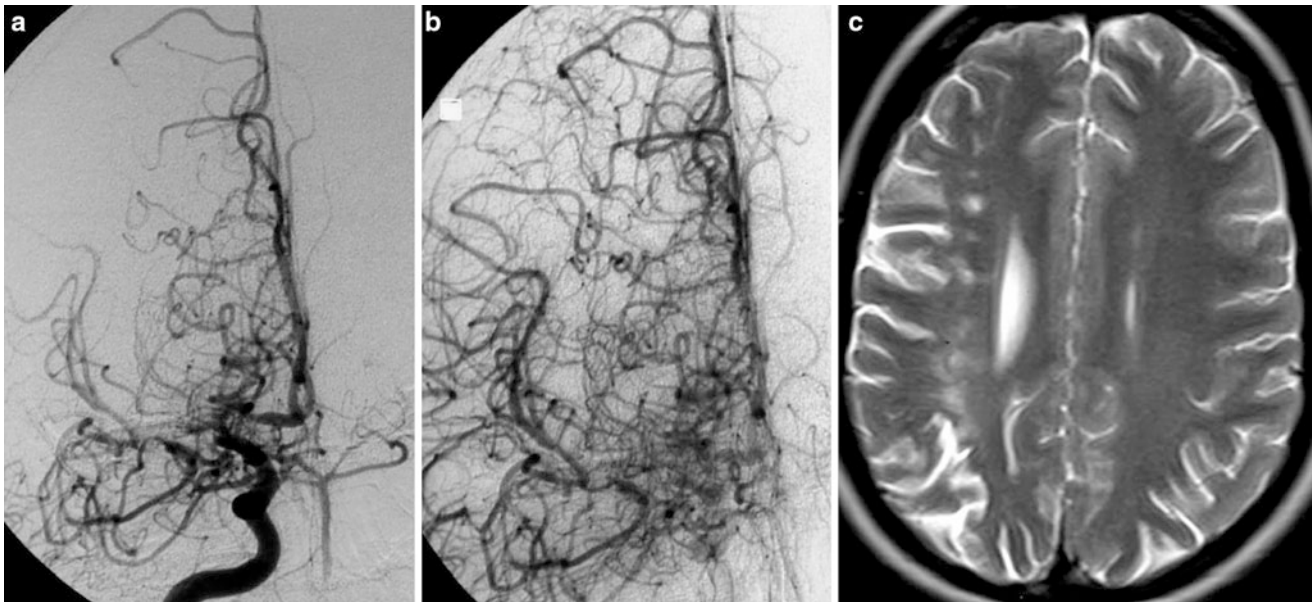


Fig. 15 Moyamoya disease. **a, b** DSA (right ICA; frontal view) at the early (**a**) and late (**b**) arterial phase shows stenoses of the proximal segments of the MCA and the ACA as well as lenticulostriate and thalamoperforate collateralization. **c** Moyamoya disease. **c** Axial T2-

weighted image demonstrates increased signal in the right hemispheric border zone due to cortical and white matter ischemic infarcts. The prominent ipsilateral sulci are due to cortical atrophy. (From Ertl-Wagner 2007)

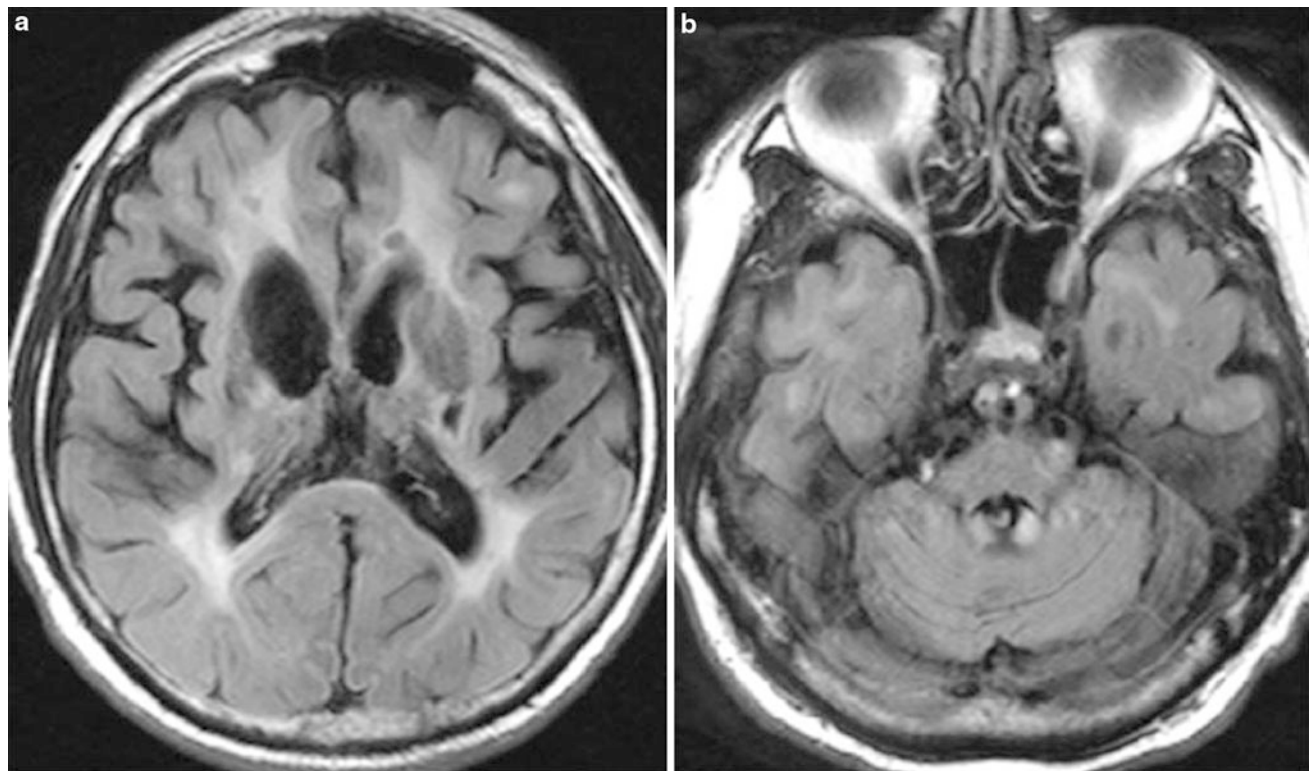


Fig. 16 Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The axial FLAIR images (**a, b**) demonstrate bilateral subcortical hyperintensities of the

anterior temporal poles. The periventricular white matter, including the external capsules, is involved as well

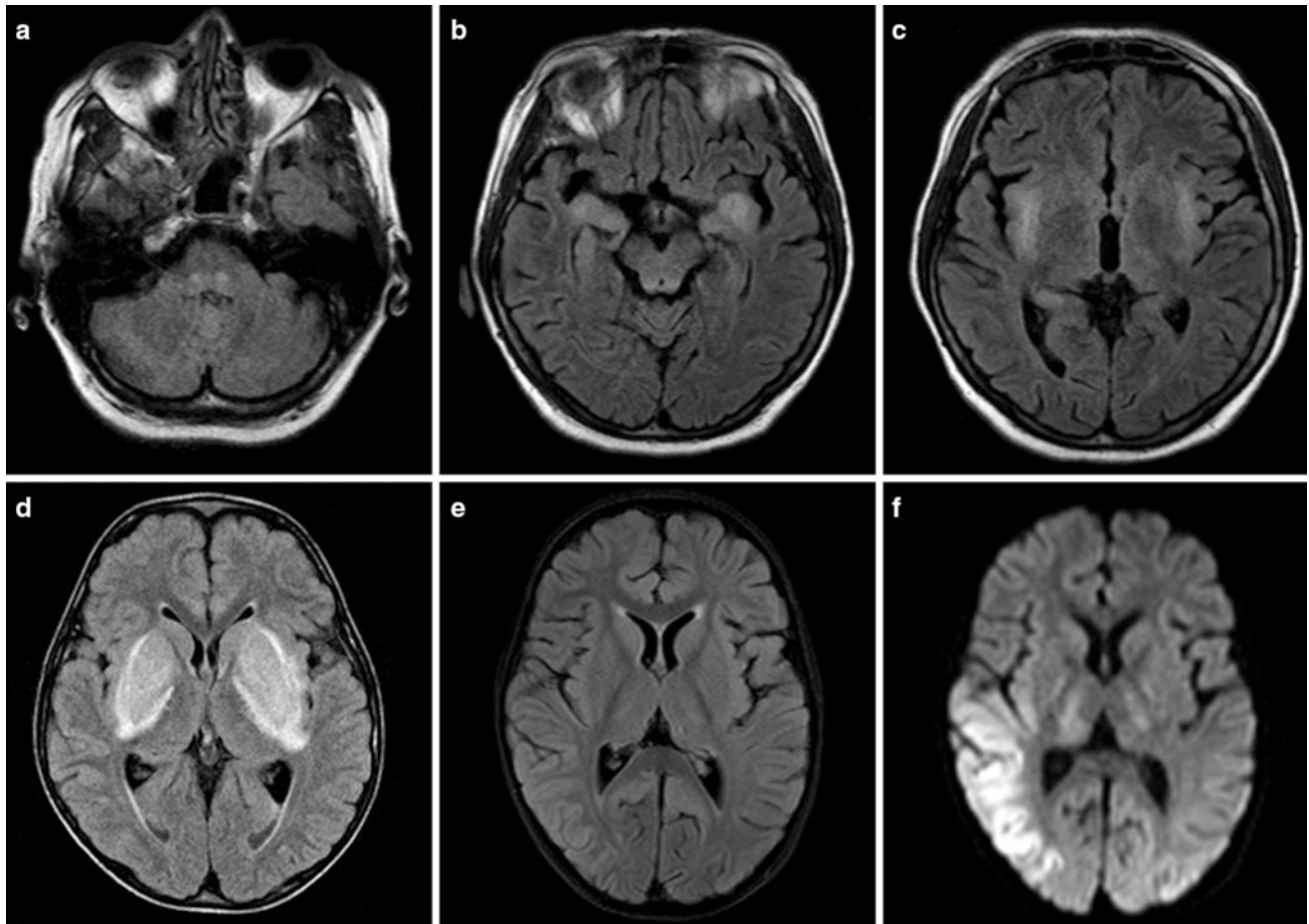


Fig. 17 HUS-associated encephalopathy. The axial FLAIR images (a–e) and the DWI image (f) show focal edematous signal changes in one adult patient (a–c) and two infants (d–f; Courtesy of A. Seitz, Pediatric Neuroradiology Heidelberg). In the pediatric population neuro-HUS typically affects bilateral basal ganglia (d) or the

occipitotemporal cortex resembling PRES (e, f). The 61-year-old woman with epidemic HUS encephalopathy demonstrated transient symmetric signal changes of the pons (a) and persistently in mesolimbic structures and thalamus (b, c)

sign”) are potentially reversible. To date, vessel wall changes on MR imaging have not been reported (Fig. 15).

2.2.5 Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

A hereditary point mutation in *Notch3* gene on chromosome 19 damages the vascular smooth muscle cells of small cerebral arteries manifesting in recurrent ischemic episodes in young adults (30–50 years). Bilateral subcortical lacunar infarcts of the anterior temporal poles are almost pathognomonic for CADASIL. Other affected regions are the superior frontal white matter and the external capsules leading to diffuse white matter hyperintensities in the course of the disease (leukoencephalopathy). As opposed to vasculitides, the cerebral cortex is mostly spared and the angiogram is usually normal (Fig. 16).

2.2.6 Radiation Vasculopathy

Radiochemotherapy can induce acute arteritis with associated transient white matter edema. Vessel wall changes due to edema and fibrosis may persist even beyond the acute stage. Chronic damage due to vasculopathy may be severe and include complete vessel obliteration, leukomalacia, calcifying microangiopathy, and brain atrophy.

2.2.7 Epidemic Hemolytic Uremic Syndrome

Hemolytic uremic syndrome (HUS) is a multisystem disorder, which is triggered by bacterial infection with entero-hemorrhagic *Escherichia coli* (EHEC). HUS sporadically affects infants and young children and is characterized by the trias of acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia. Central nervous system complications may occur in up to 50 % and pediatric neuroimaging usually demonstrates bilateral, symmetric lesions of basal ganglia or

extensive cortical and/or subcortical lesions which might resemble Posterior Reversible Encephalopathy Syndrome (PRES). The clinical outcome is generally good.

In adults, however, HUS occurs only rarely and is not associated with neurological complications. Having said that, the recent EHEC epidemic in Northern Germany in May/June 2011 affected as many as 3,800 patients. Those who developed HUS were mainly female adults, who developed neurological complications in about 50 %. Neuroimaging revealed mainly transient vasogenous edema of the pons as well as (persistent) supratentorial signal changes in the thalamus, mesolimbic structures and subcortically (Wengenroth et al. 2012; Fig. 17).

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