Diagnosis and treatment of cerebral vasculitis

Peter Berlit

Abstract: Vasculitides are characterized by inflammation and necrosis of the blood vessel wall. Large vessels including the aorta are affected in giant-cell arteritis, medium-size arteries in classic polyarteritis nodosa. The small-vessel vasculitides are separated in those with antineutrophil cytoplasm antibodies (ANCA) and those without. The primary angiitis of the central nervous system (PACNS) is a rare disorder affecting both medium- and small-sized vessels. Major symptoms of cerebral vasculitis are stroke, headache and encephalopathy. Diagnosis is based on laboratory and imaging findings. When cerebral affection occurs in systemic vasculitis an acute inflammatory response with raised erythrocyte sedimentation rate and increased values of C-reactive protein is present. In many cerebral vasculitides including PACNS, CSF studies reveal inflammatory findings. Magnetic resonance imaging, including ADC maps, diffusion and gradient echo sequences, is the investigation of choice to detect and monitor cerebral involvement. Certain MRI techniques and 18-fluorodeoxyglucose positron emission tomography allow the visualization of vessel wall inflammation when the lumen is still unaffected on angiography. The treatment recommendations for cerebral angitis are derived from protocols for systemic vasculitides. In general, a combination of steroids and pulse cyclophosphamide (CYC) is recommended for induction treatment. An alternative option is the use of the anti- CD20 antibody rituximab. Methotrexate, azathioprine and mycophenolate mofetil are recommended as alternatives to CYC once remission is achieved.

Keywords: Vasculitis, angiitis, stroke, angiography, antibodies, immunosuppressants, giant cell arteritis, steroids

Introduction

Vasculitides constitute a heterogeneous group of diseases characterized by inflammation and necrosis of the blood vessel wall. According to the Chapel Hill Consensus Conference (CHCC) the primary systemic vasculitides may be classified into three main groups: those affecting predominantly large-sized vessels, medium- and small-sized vessels, respectively [Jennette and Falk, 2007]. In addition, histological, pathogenic aspects and clinical presentation should be taken in account (Table 1). This paper focuses on systemic vasculitides with possible cerebral involvement and the primary angiitis of the central nervous system (PACNS).

Large vessels including the aorta are affected in giant cell arteritis (GCA). Histologically, there are granulomas with giant cell formation. If patients are more than 50 years old, temporal arteritis is considered, in the age group under 50 years Takayasu's disease may be suspected. Medium-size arteries are involved in Kawasaki syndrome of childhood and in classic polyarteritis nodosa (PAN). A mucocutaneous lymph node syndrome is present in the Kawasaki syndrome but not in polyarteritis. Cerebral involvement may occur in PAN, but is very unusual in Kawasaki syndrome [Tabarki *et al*. 2001].

All other systemic vasculitides affect small vessels. The small vessel vasculitides may be separated in those with antineutrophil cytoplasmic antibodies (ANCA) and those without. Some also present immune complex deposits in the vessel wall. ANCA-positive vasculitides include the Churg–Strauss syndrome (CSS; allergic granulomatosis) with symptoms of asthma and eosinophil granulomas. Wegener granulomatosis (WG) presents with granulomas of the upper airways and renal involvement, but no asthma. The microscopic variant of polyarteritis represents an angiitis without granulomas or asthma. Both CSS and microscopic polyangiitis are associated with pANCA/MPO. cANCA/PR3 are present in WG. Because of the paucity of immune deposits, WG, microscopic polyangiitis (MPA) and CSS are often referred to as PSV

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Table 1. Classification of primary vasculitides.

Vessel size	Granulomatous	Nongranulomatous
Large	Giant cell arteritis: Cranial arteritis Takayasu arteritis	
Medium		Polyarteritis nodosa Kawasaki disease
Small (with ANCA)	Wegener granulomatosis Churg–Strauss syndrome	Microscopic polyarteritis
Small (with immune complexes)		Cryoglobulinemic vasculitis Behçet syndrome

(pauci-immune systemic vasculitis). Immune complex deposits are seen in the vasculitic variants of systemic lupus erythematosus (SLE) and rheumatoid arthritis, and with cryoglobulinemic angiitis. A four-step algorithm in order to categorize patients with WG, MPA, CSS and PAN for epidemiological studies into single clinically relevant categories was developed by Watts *et al.* [2007] based on the ACR criteria and the CHCC definition.

The isolated vasculitides of the nervous system are not definitely classified yet. PACNS may affect both medium-sized and small vessels, with or without granulomas. The isolated angiitis of the peripheral nervous system affects small vessels without ANCA, but in part with immune complex deposits into the vessel wall [Davies *et al.* 1996].

Frequency
Cranial arteritis is the most frequent form of vasculitis affecting persons over 50 years of age. In Europe prevalences of 15–30/100,000 and an incidence of 18/100,000 have been reported. Systemic vasculitides in general are rare diseases. The introduction of prednisone and cyclophosphamide (CYC) for the treatment of these progressive and life-threatening disorders improved survival dramatically [Andrassy *et al.* 1991]. In epidemiological studies, the prevalence of the medium- and small-vessel vasculitides has increased during the last decade [Selga *et al.* 2006]. A probable explanation is the improvement of long-term survival achieved. Mohammad *et al.* [2007] found a prevalence of the small vessel vasculitides close to 300 per million adults in Sweden. In Germany, the incidences of antineutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitides (Wegener's granulomatosis [WG], microscopic polyangiitis [MPA] and Churg–Strauss

syndrome [CSS]) were calculated at about 9.5 per 1,000,000 annually, with the incidence of WG being two to three times greater than those of MPA and CSS [Reinhold-Keller *et al.* 2002]. Gibson *et al.* [2006] reported a 5-year prevalence for WG of 131 per million and for MPA of 93.5 per million, respectively. For PAN, an annual incidence of 1.6 per million has been described [Selga *et al.* 2006]. Isolated cerebral angiitis is even rarer than any of the systemic vasculitides. About 700 cases have been published worldwide [Salvarani *et al.* 2007; Schmidley, 2000].

Diagnosis
Major symptoms of cerebral angiitis are stroke, headache and encephalopathy. Other symptoms include seizures, cranial nerve palsies or myelopathies. Inflammatory signs and symptoms in particular may lead to the early suspect of vasculitis. The differential diagnosis includes a wide range of conditions, such as degenerative vasopathies, embolic diseases, or coagulation disorders.

Laboratory findings suggestive of a systemic vasculitis include an acute inflammatory response with raised erythrocyte sedimentation rate (ESR) and increased values of C-reactive protein (CRP). Anemia, thrombocytosis, elevated liver enzymes and low complement are frequent associated findings. Complement consumption preferentially is present in vasculitides associated with immune complexes. If a cerebral manifestation occurs in the course of a systemic vasculitis, an acute inflammatory response has to be expected. In PACNS, serum findings usually are normal, but CSF studies reveal inflammatory findings. These include a mild lymphomonocytic pleocytosis or protein elevation in more than 90% of patients [Schmidley, 2000]. Laboratory tests in suspected vasculitis should search for systemic inflammation including specific antibodies, but must also exclude important differential diagnoses (Box 1).

Imaging techniques play a crucial role in securing the diagnosis of a vasculitis, and in demonstrating cerebral involvement. In large-vessel angiitis, conventional digital subtraction angiography (DSA) is the gold standard for the demonstration of vessel stenoses or aneurysms [Alhalabi and Moore, 1994]. MRI performed with and without contrast medium is the investigation of choice to detect and monitor cerebral involvement [Pipitone and Salvarani, 2008]. Measurements should include ADC-maps, diffusion and

Box 1. Laboratory tests in suspected vasculitis.

Erythrocyte sedimentation rate, C-reactive protein, blood cell differentiation, liver enzymes, creatinine, glomerular filtration rate, coagulation tests with search for coagulopathies [especially anticardiolipin-antibodies, lupus anticoagulant], electrophoresis, creatinine kinase, lactate dehydrogenase, haptoglobulin, ferritine, angiotensin converting enzyme, immunofixation, quantitative evaluation of immunoglobulins, search for cryoglobulins, TSH, thyroid antibodies, rheuma factor, antinuclear antibodies [ANA], ds-DNA antibodies, histon antibodies, complement, anti-Ro [SS-A] and anti-La [SS-B-] antibodies, c- and pANCA/MPO [myeloperoxidase [MPO]], anti-endothelial antibodies, drug-screening, blood cultures
Serologic tests for syphilis, borreliosis, hepatitis B and C, HIV
Urine examination including electrophoresis
CSF: cell differentiation, isoelectric focussing, cultures, antigens, PCR [viruses, bacteria, mykosis]

perfusion measurements and gradient echo sequences. In cerebral vasculitis, both ischemic and hemorrhagic lesions of different ages as well as findings of focal or diffuse inflammation are observed [Pomper et al. 1999].

Colour duplex sonography, computerized tomography angiography (CTA), and magnetic resonance imaging (MRI) with magnetic resonance angiography (MRA) may show vessel wall alterations when the lumen is still unaffected on angiography. 18-fluorodeoxyglucose positron emission tomography (PET) is very sensitive in revealing inflamed vessels [Both et al. 2008]. In suspected vasculitis, it is especially important to search for cryoglobulinemia and drug-induced angiitis. Possible drug associations include thiouracil, allopurinole, minocycline, penicillamine, carbamazepine, phenytoine, MTX and isotretinoine [Holder et al. 2002].

Giant cell arteritis (GCA)

Cranial or temporal arteritis (TA) is a chronic, granulomatous vasculitis of large- and medium-sized arteries. Women are affected more frequently than men (3 : 1 to 5 : 1). Mean age at the beginning of the disorder is 65 years or more. Genetic predisposition has been reported with an association to the human leukocyte antigen (HLA)-DRB1 molecule.

Clinically, TA may present with symptoms related to the involved cranial vessels, by the signs of a systemic illness with fever, malaise and weight loss or by polymyalgia rheumatica. Neurological symptoms include the new onset of a persisting headache, possibly with jaw claudication, visual symptoms, such as diplopia, flimmer scotoma and amaurosis fugax, with blindness as a dreaded complication, or rarely stroke [Salvarani et al. 2006].

Laboratory findings reveal a raised ESR and increased values of CRP. This acute phase response is induced by pro-inflammatory cytokines, mainly interleukins (IL) 1, 6 and tumor necrosis factor (TNF) alpha. These are produced by activated macrophages in the vessel wall. The target antigen of the CD4+ T cell immune response in GCA is probably located in the internal elastic layer of the vessel wall which explains that arteries of the anterior intracerebral circulation are infrequently affected because these lack an internal elastic layer [Weyand and Goronzy, 1999]. On clinical examination, a tenderness or decreased pulsatility of the temporal arteries is frequent. Colour duplex sonography may show a dark halo as a characteristic finding in TA. Contrast-enhanced, high-resolution MR imaging allows noninvasive assessment of the mural inflammation [Bley et al. 2007].

The definitive diagnosis of TA requires the pathologic demonstration of a vasculitis with mononucleated cell infiltrates of all mural layers and occurrence of giant cells on a temporal artery biopsy (Box 2). The degree of intimal hyperplasia on histology findings is associated with neuro-ophthalmic complications [Makkuni et al. 2008]; the presence of giant cells in particular is associated with permanent visual loss [Chatelain et al. 2009].

High-dose corticosteroids are the only effective therapy in TA. Prednisone or prednisolone (Pred) at a daily dose of 1 mg per kg should be started immediately in suspected TA. Corticosteroid treatment must not be delayed by temporal artery biopsy. The biopsy is positive even after a few days of steroid treatment. The clinical symptoms improve rapidly, usually within a few days. As soon as the acute phase reactants have returned to normal, tapering of the steroids may begin. Usually, a daily dose of 30 mg prednisone is reached within 4 weeks. Tapering should then be performed cautiously by no more than 2.5 mg every 2 weeks. When a daily dose of 15 mg is reached, dose reduction should not

exceed 1 mg per month. Whenever symptoms or acute phase proteins recur during tapering, the last effective dose plus 10 mg should be administered. The majority of patients require corticosteroid treatment for a time period of more than 2 years. In order to avoid side effects all patients should receive aspirin, pantoprazole, calcium and vitamin D [Nesher *et al.* 2004].

Up to 80% of patients with TA experience complications related to steroid therapy. These include diabetes mellitus, osteoporosis with vertebral compression fractures and Cushing syndrome. The addition of steroid sparing immunosuppressive agents like methotrexate (MTX) may be tried, especially in diabetics, but has not been proven to be clearly beneficial [Hoffman *et al.* 2002; Jover *et al.* 2001]. In small trials, infliximab and etanercept have been evaluated in patients with TA and toxicity secondary to steroid therapy. The results showed a slight but nonsignificant effect [Martínez-Taboada *et al.* 2008; Hoffman *et al.* 2007].

Box 2. Diagnostic criteria of temporal arteritis.

Three of the five diagnostic criteria for giant cell arteritis have to be met [Hunder *et al.* 1990]
1 Age 50 years or more
2 New developed headache
3 Tenderness of the superficial temporal artery
4 Elevated sedimentation rate, at least 50 mm/h
5 Giant cell arteritis in a biopsy specimen from the temporal artery

The ischemic complications of TA such as blindness and stroke result from luminal narrowing of the affected arteries, which may be demonstrated by DSA (Figure 1). Approximately 4% of patients with TA experience transient ischemic attacks (TIA), or stroke, more frequently in the posterior circulation than in the carotid territory. Almost all patients with TA-associated strokes have a significant acute phase response with elevated ESR and CRP. The mortality has been reported to be as high as 75% [Kumar and Costa, 2007]. The impact of cardiovascular risk factors on the occurrence of cerebral ischemic events has been evaluated in the Reggio Emilia region of Italy in patients with biopsy-proven TA. Both a history of hypertension or ischemic heart disease were associated with a higher risk of stroke [Salvarani *et al.* 2009]. In the case of a vascular emergency in TA (blindness, stroke), we start therapy with 1000 mg of prednisone daily for 5 days, followed by oral treatment at a dose of 1 mg per kg body weight [Hayreh *et al.* 2002; Staunton *et al.* 2000].

Takayasu's arteritis

The second variant of giant cell arteritis (GCA) affects people younger than 50 years. Takayasu's arteritis is a rare granulomatous panarteritis of the aorta and its major branches resulting in localized stenoses, vascular occlusion and aneurysm formation. The disease starts with nonspecific systemic signs and symptoms such as arthralgia, fever, fatigue, headaches, rashes and weight loss. But usually diagnosis is delayed until the
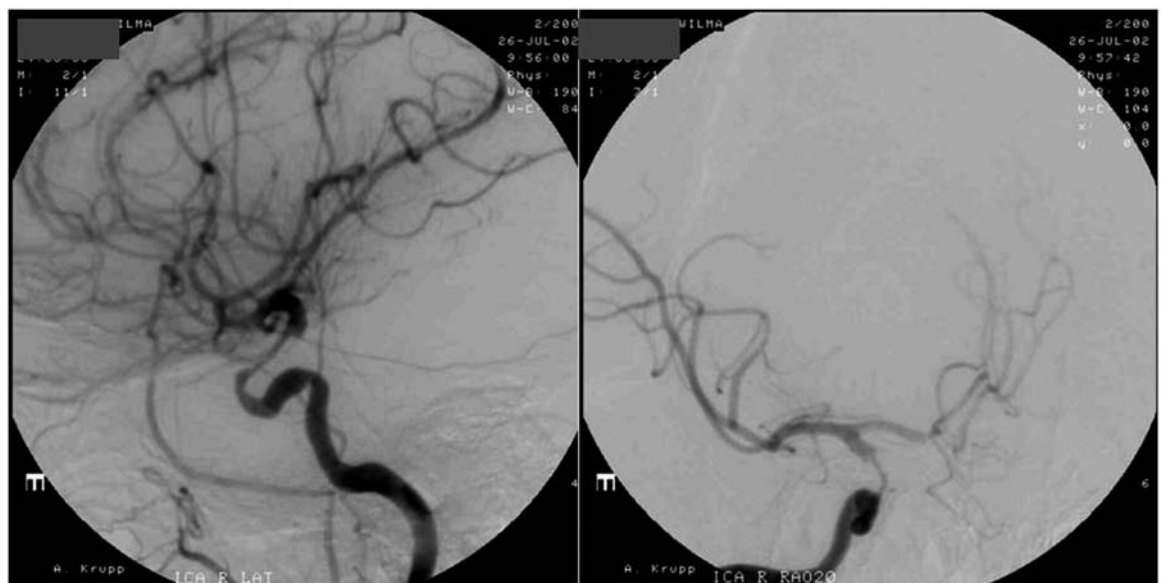

Figure 1. Angiography findings in cranial arteritis. The patient presented with a hemiparesis on the left.

occlusive stage leads to ischemic symptoms of the extremities or to stroke. On clinical examination, systolic blood pressure differences of more than 10 mmHg between both arms and decreased brachial artery pulse (pulseless disease) are typical findings (Box 3).

In Takayasu's arteritis there are no specific laboratory abnormalities. An elevation of ESR or CRP and a mild anaemia are possible, but the acute phase response may be normal even in the early inflammatory stages. Anti-endothelial antibodies (AEA) have been reported but are not an obligatory finding. Aortic biopsy specimens often reveal histological evidence of ongoing vascular inflammation in patients with entirely normal laboratory findings.

DSA still is the gold-standard investigation for the diagnosis of Takayasu's arteritis (Figure 2). Besides conventional angiography, MRI and MRA, CT angiography, PET and high-resolution ultrasound are used more frequently for the investigation of Takayasu's arteritis [Andrews and Mason, 2007]. Especially delayed contrast-enhanced MRI sequences and abnormal ^{18}F-FDG-PET uptake are able to detect vascular inflammation in the prestenotic phase, if the diagnosis is considered early enough [Yamada *et al.* 2000].

Fifty percent of patients respond to corticosteroid therapy alone in early phases of the disease. MTX or AZA are frequently used as an alternative to oral CYC as immunosuppressants. Mycophenolate mofetil (MMF) and anti-TNF therapy have also been studied in small series [Molloy *et al.* 2008].

It is important to treat the associated renovascular hypertension of Takayasu's arteritis with angiotensin II receptor antagonists. Concomitant therapies include low-dose aspirin and statin even in normolipidemic patients. Unfortunately, in later stages stenotic lesions often persist in spite of combined drug treatment. An interventional approach in Takayasu's arteritis should only be considered if stenotic or occlusive lesions lead to

Box 3. Modified American College of Rheumatology criteria for the diagnosis of Takayasu's arteritis.

Takayasu's arteritis may be diagnosed when at least three of these six criteria are present (sensitivity of 90.5% and a specificity of 97.8%) [Arend *et al.* 1990]
1 Age at disease onset <50 years
2 Claudication of extremities
3 Decreased brachial artery pulse
4 Blood pressure [systolic] difference > 10mmHg between arms
5 Bruit over subclavian arteries or abdominal aorta
6 Arteriographic narrowing or occlusion of the aorta, its primary branches or large arteries (not due to arteriosclerosis, fibromuscular dysplasia or similar causes)
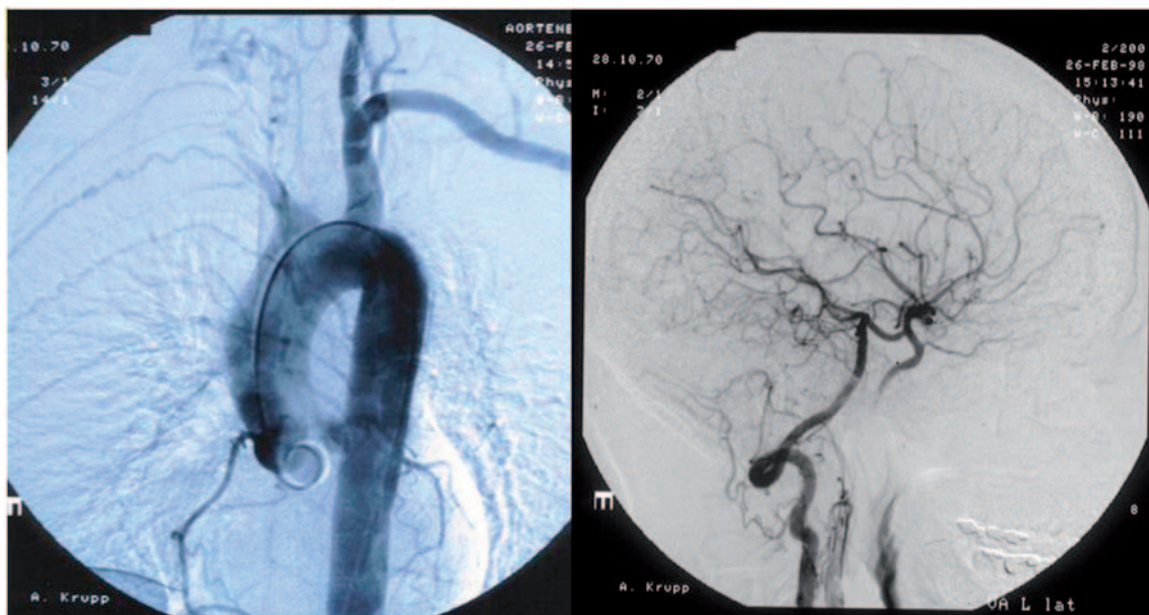

Figure 2. Takayasu disease in a 28-year-old woman who presented with mild stroke symptoms after a syncope. Angiography revealed occlusions of the brachiocephalic trunk and the left common carotid artery.

significant hemodynamic effects, or if aneurysmal enlargement results in the risk of rupture or dissection [Miyata *et al.* 2003].

Polyarteritis nodosa (PAN)

According to the Chapel Hill Consensus Conference (CHCC) on the nomenclature of systemic vasculitides classical PAN should be restricted to a systemic necrotizing vasculitis of medium-sized arteries without the involvement of smaller vessels. The microscopic form of polyarteritis associated strongly with pANCA/MPO should be separated from the classical disease. PAN may be associated with hepatitis virus (HV) infection. PAN with and without HV association differ in aspects of clinical course, outcome and response to treatment; peripheral nerve involvement in particular is more prevalent in HV-associated PAN [Cacoub *et al.* 2001]. The diagnostic criteria of the American College of Rheumatology are still used for clinical purposes (Box 4). But these are reliable only after exclusion of all other forms of vasculitis.

The majority of patients present signs of a systemic illness with fever, malaise and weight loss, accompanied by arthritis and skin signs. Acral necroses and severe peripheral ischemia are characteristic. Myalgias and a polyneuropathy of the multiplex type are very frequent neurological features. A combined biopsy of muscle and nerve demonstrates the necrotizing granulomatous inflammation [Khellaf *et al.* 2007].

Brain involvement has been reported in up to 20% of patients in the monograph by Schmidley [2000]. But since most of the cited reports were performed before the Chapel Hill classification criteria were developed the true

Box 4. American College of Rheumatology classification of polyarteritis nodosa.

PAN may be diagnosed with three of these ten criteria (82% sensitivity, 86% specificity), if other vasculitides are excluded
1   Loss of weight >4 kg
2   Livedo reticularis
3   Testicular pain
4   Myalgias
5   Mononeuritis or polyneuritis
6   Blood pressure elevation >90 mmHg
7   Creatinine >1,5 mg/dl
8   Hepatitis B or C virus antibodies
9   Pathologic arteriography (aneurysm, occlusions)
10   Typical histology finding

number is lower. Ischemic stroke, hemorrhages and a progressive encephalopathy with or without seizures may occur. In PAN with negative hepatitis serology, induction treatment is started with prednisone and CYC. In emergency situations plasmapheresis may be tried. In HV associated PAN prednisone is combined with virustatics like lamivudine (in hepatitis B) or interferone-alpha and ribavirine (in hepatitis C), a plasmapheresis is possible in acute situations.

Wegener's granulomatosis (WG)

This rare small vessel arteritis is frequently associated with cANCA/PR3 and sometimes with MPO-ANCA. Men are affected twice as often as women. In the limited stage of the disease, necrotizing granulomas of the nose and the paranasal sinuses may lead to compression of neighborhood structures with cranial nerve lesions, diabetes insipidus or exophthalmus. A nonseptic meningitis with enhancement of the basal meninges especially of the tentorium in MRI and the development of an occlusive or communicating hydrocephalus are possible. With generalization, the systemic necrotizing vasculitis involving small arteries and veins leads to affections of the lung and kidney (ELK-criteria: ear nose throat, lung, kidney). cANCA/PR3 are present in 70% of patients with limited WG and in >90% of systemic WG cases. The diagnostic criteria of the American College of Rheumatology are listed in Box 5.

With generalization, polyneuropathies, myelopathies and cerebrovascular neurological symptoms frequently occur. Neurologic involvement in WG has been described in 22–33.6% of patients [Nishino *et al.* 1993; Fauci *et al.* 1983]. Brain involvement presents with ischemic stroke, hemorrhages and encephalopathy with or without seizures.

Pred and CYC are the remission induction therapy of choice in generalized WG. Fauci *et al.*

Box 5. American College of Rheumatology criteria for the diagnosis of Wegener granulomatosis.

Diagnosis with two of four criteria possible (sensitivity 85%, specificity 92%)
1   Necrotizing ulcerating inflammation of nose, sinuses, mouth, or pharynx
2   Irregular lung infiltrates
3   Nephritis
4   Granulomatous vascular and perivascular inflammation

[1983] described the first protocol with a daily dose of oral CYC 2 mg/kg body weight and prednisone 1 mg/kg, respectively. Pred was tapered after 2–4 weeks. Though very efficient, complications of this treatment are severe. Life threatening infections and an ovarian insufficiency occur in up to 50%, a hemorrhagic toxic cystitis in 40%. The risk of bladder cancer is 30-fold increased, the risk of a secondary lymphoma 10-fold. Therefore other induction protocols have been developed in order to reduce the cumulative CYC dose. With parenteral CYC 15 mg/kg infusions every month (pulse CYC) about 15 g/year are given compared to 35 g/year with the standard Fauci protocol (100 mg/350 days). Since the risks of bladder toxicity and a myelodysplastic syndrome (MDS) increase dramatically with a cumulative CYC dose of > 30 g, higher doses should be strictly avoided [Faurschou *et al.* 2008; Knight *et al.* 2004]. Supportive therapies with pulse CYC include antiemetics, bladder protection with NaCl infusions and uromitexane perfusor. An effective ovarian protection is necessary. Alternative induction treatment options include MTX 20–25 mg per week [Bosch *et al.* 2007] or rituximab [Keogh *et al.* 2006].

After successful induction therapy AZA is as effective as CYC. Alternatively, other immunosuppressants like MMF have been tested in smaller studies. After remission or in the limited stage of the disease, the combination of 2×800 mg sulfamethoxazol and 2×160 mg trimethoprime may be sufficient [Stegeman *et al.* 1996].

Relapses are associated with the presence of cANCA/PR3, target organ involvement and the choice of treatment. The presence of ANCA at diagnosis, cardiac or renal involvement increase the risk of relapses. Patients receiving <10 g CYC in the first 6 months show an increased relapse rate. Adjunctive trimethoprim/sulfamethoxazole maintains remission for longer [Mukhtyar *et al.* 2008]. Survival also depends on age at diagnosis and renal involvement [Guillevin *et al.* 1997].

Churg–Strauss syndrome (CSS)
Churg–Strauss syndrome (CSS) is the rarest of the necrotizing small-vessel vasculitides. Clinically patients present with a history of allergic diathesis and asthma, pathologic hallmark of the disease are eosinophil-rich granulomas. pANCA/MPO are present in 40% of patients [Sable-Fourtassou *et al.* 2005]. These show an increased frequency of renal, lung and central nervous system [CNS] involvement. Patients without ANCA present more frequently with cardiac disease [Grau, 2008].

In ANCA-positive patients, polyneuropathies are of the multiplex type and associated with the histologic detection of small vessel vasculitis. Symmetrical polyneuropathies possibly caused by eosinophil infiltrates are seen in the ANCA-negative group [Chao *et al.* 2007]. CNS involvement is observed in 6–8% of patients with cerebral infarctions, intracerebral hemorrhages and subarachnoid hemorrhages being the most frequent manifestations [Sehgal *et al.* 1995].

The five factor score (proteinuria > 1 g/day, creatinine > 1.58 mg/dl, gastrointestinal involvement, cardiomyopathy, neurological involvement) was introduced in order to facilitate treatment decisions and evaluate prognosis. The absence of any of the five factors carries a good prognosis [Lane *et al.* 2005; Keogh and Specks, 2003]. These patients may be treated with prednisone alone. The presence of two or more of the factors increases the risk of mortality; these patients need a combined induction therapy with CYC and steroids. The remission rate is 80–90%. Relapse rates are about 35% at 2 years. Patient survival varies between 60% and 97% at 5 years [Mukhtyar *et al.* 2008].

Behçet's disease
Behçet's disease is a multisystem, chronic-relapsing vasculitis affecting predominantly the venous system. The rare disorder is more prevalent in the Middle East, Far East and the Mediterranean. According to the criteria of the International Study Group for Behçet's Disease [Akman-Demir *et al.* 1999], recurrent oral ulcerations must be present in combination with at least two of the following: recurrent genital ulceration, eye lesions (uveitis, cells in the vitreous on slit lamp examination or retinal vasculitis), skin lesions (erythema nodosum) or a positive pathergy test result. For pathergy testing a skin lesion is produced with a sterile needle. If an erythematous papule develops as a sign of skin hyperreactivity within 48 hours the test is positive. The diagnosis of Behçet's disease is entirely based on clinical grounds since no pathognomonic laboratory or histologic findings exist. Increased concentrations of antibodies against

phosphatidylserine and ribosomal phosphoproteins have been described [Berlit *et al.* 2005].

Recurrent oral and genital ulcers are frequently the only symptoms at the onset of the disease. CNS involvement (Neuro–Behçet or NB) occurs in about 30% of patients after an average of 5 years. Of these, 80% present parenchymal NB with motor tract signs, stroke and headache (Figure 3). Frequently, the brainstem is predominantly involved [Mirsattari *et al.* 2004]. Pseudotumour is the most frequent presentation of sinus thrombosis and present in 20% of NB patients. Only 3% of patients develop neurologic symptoms without mucocutaneous lesions or ocular symptoms [Akman-Demir *et al.* 1999].

Prognosis depends largely on the presence of manifestations affecting the blood vessels, CNS and gastrointestinal system. Controlled studies for the treatment of the mucocutaneous manifestations exist for colchicine, thalidomide, dapsone, AZA, interferon-alpha and etanercept. AZA was significantly better than placebo in preventing the development of ocular disease [Yazici *et al.* 1990].

Whether these substances also are effective in treating CNS manifestations has not been studied in larger trials. In NB, combinations of high doses of corticosteroids and immunosuppressive drugs are recommended. Prednisone is started with daily parenteral pulses of 1000 mg for 3–5 days followed by oral therapy starting at 1 mg/kg daily. Maintenance oral corticosteroids should be tapered over 2–3 months. For the treatment of sinus thrombosis corticosteroids in combination with oral anticoagulation are recommended [Barnes, 2006].

CYC, MTX, interferon-alpha, or AZA (up to 3 mg/kg) may be used as immunosuppressive agents in parenchymal NB. Because of its potential neurotoxicity, ciclosporine A should not be used in the treatment of NB patients. Chlorambucil should be avoided because of its myelotoxicity and increased risk of malignancies [Hatemi *et al.* 2008]. In NB patients refractory to these treatments, or in the case of relapses while on maintenance treatment, infliximab or etanercept may be tried [Sfikakis *et al.* 2007].

Primary angiitis of the central nervous system (PACNS)

The diagnosis of PACNS may be considered with symptoms of a multifocal or diffuse CNS disorder with remitting or progressive course, cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) findings supporting the diagnosis of vasculitis, and finally either an angiography with a vasculitic pattern or a leptomeningeal and parenchymatous biopsy proving vasculitis. Criteria for the diagnosis (Box 6) were suggested in 1987 [Calabrese and Mallek, 1987].

PACNS is a rare disease with approximately 700 cases published worldwide [Berlit, 2009a]. CNS manifestations include headache, strokes, seizures, myelopathy, and encephalopathy.
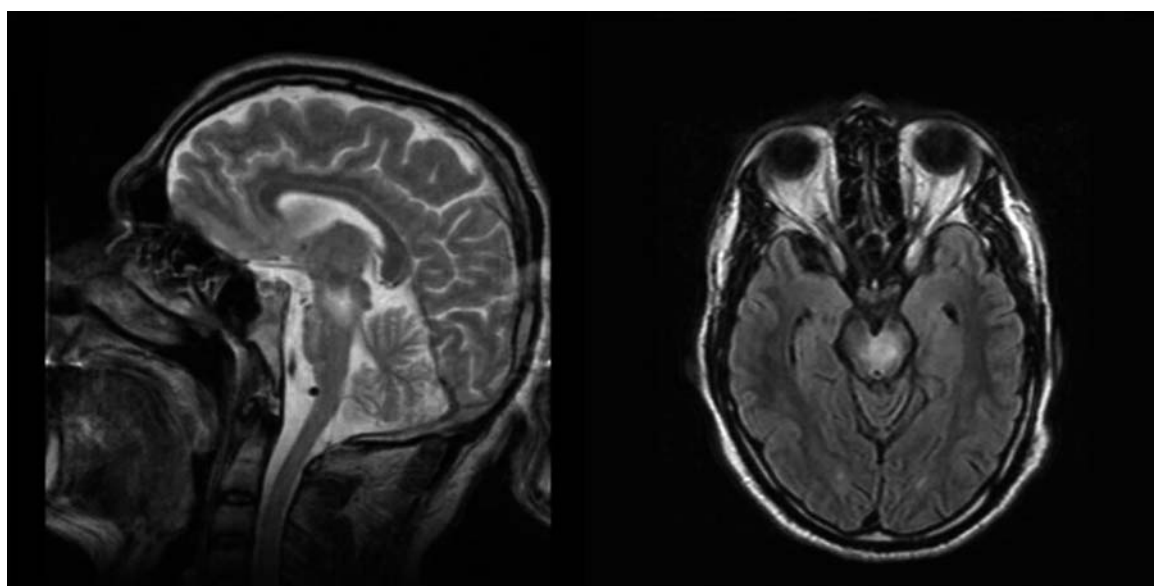

Figure 3. Example of MRI findings in Neuro-Behçet (sagittal T2w and axial FLAIRw).

Usually, symptoms develop gradually over weeks, with a fluctuating or stepwise progressive course. While mild systemic symptoms or an elevated CRP are possible in PACNS, organ manifestations other than the CNS are an exclusion criterion for the diagnosis.

Neither neuroradiological findings nor laboratory tests allow a definite diagnosis of the disorder. In the majority of published case series of PACNS, abnormal CSF-findings have been reported [Schmidley, 2000]; both a CSF pleocytosis and a protein elevation are frequent. Repeated CSF examinations in the course of the disease are almost never completely normal. Cultural and serological CSF examinations are essential for the exclusion of infections [Berlit, 2009b; 2004b]. MRI may demonstrate ischemic and hemorrhagic lesions of different ages, leukencephalopathies, tumor-like lesions, or gadolinium enhancement of the meninges (Figure 4). Isolated myelopathies have also been reported [Salvarani *et al.* 2008].

Angiography sometimes demonstrates bilateral vessel stenoses or occlusions consistent with an angiitis (Figure 5). On the other hand, many patients with histologically proven PACNS have an entirely normal angiogram [Schmidley, 2000]. The angiographic pattern considered diagnostic

Box 6. Diagnostic criteria for the diagnosis of primary angiitis of the central nervous system.

1. Acquired neurological deficit unexplained after complete evaluation
2. Diagnostic cerebral angiogram with narrowing of vessels, areas of dilation and/or beaded vessel appearance, displacement of vessels or vessel occlusions
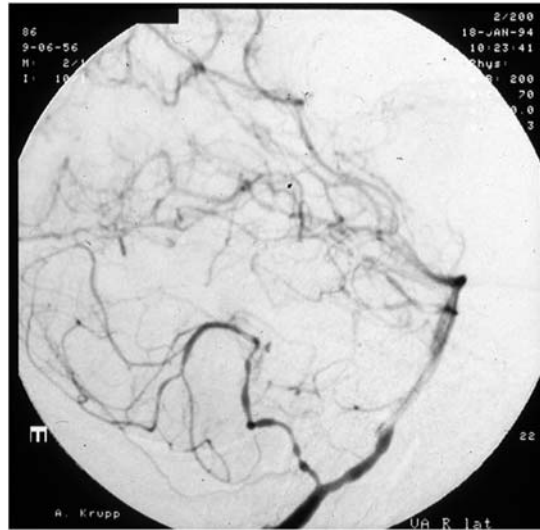3. No evidence of systemic vasculitis or any other condition that could mimic the angiogram findings

Figure 5. Vasculitic pattern on angiography. Note the multilocular narrowing of large- and medium-sized vessels.
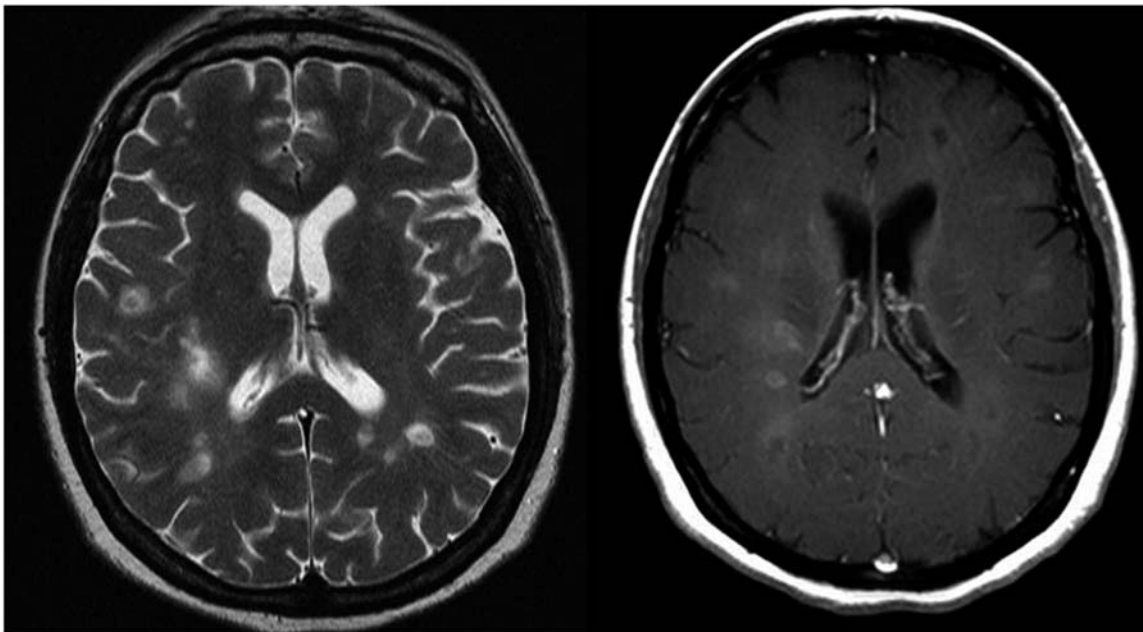

Figure 4. Example of MRI findings in cerebral vasculitis (T2w and T1w after gadolinium).

of vasculitis is often caused by reversible vasoconstriction syndromes associated with drugs, migraine, hypertension, eclampsia or the postpartum period [Calabrese *et al.* 2007]. Neoplastic diseases and spasms after subarachnoid hemorrhage or angiography are further important differential diagnoses. The more benign course of reported PACNS cases diagnosed on the basis of angiography alone may be an indicator for the heterogeneity of syndromes involved.

A brain and leptomeningeal biopsy demonstrating angiitis remains the gold standard for the diagnosis of PACNS. Open biopsies performed in recent MRI lesions are especially diagnostic. If there are no lesions accessible for surgery in noneloquent brain areas, a biopsy from the right frontal lobe is recommended [Moore, 1989]. The histologic findings of PACNS consist of granulomatous inflammation, fibrinoid necrosis of vessel walls or exclusively lymphocytic cellular infiltrates. There was no correlation between the histologic pattern and clinical manifestations or prognosis [Salvarani *et al.* 2008].

Based on the findings of 105 patients with suspected PACNS, a differentiation in small- and medium-vessel disease was suggested [MacLaren *et al.* 2005]. In this study, medium-vessel PACNS was compared with systemic PAN, had a benign course with isolated episodes and only rare relapses, and DSA with MRI was considered diagnostic. On the other hand, there were normal DSA findings in the small-vessel variant which showed a progressive course with frequent relapses and was compared with the microscopic variant of systemic polyarteritis by the authors. But in their retrospective series of 101 patients diagnosed by DSA ($n = 70$) or biopsy ($n = 31$), Salvarani *et al.* [2008] observed relapses more frequently in medium- and large-vessel than in small-vessel variants of the disease. Whether angiographically defined medium- and small-vessel PACNS really are variants with a different prognosis remains unclear.

No controlled therapy studies for CNS angiitis have been performed yet. The treatment recommendations for PACNS are derived from the protocols for systemic vasculitides with severe organ involvement. In general, a combination of steroids and pulse CYC is recommended. But before CYC is given, the exclusion of a systemic infection is essential. Infectious diseases resembling PACNS include spirochetal (neurosyphilis,

borreliosis), rickettsial (typhus, Rocky Mountain spotted fever) and viral (varicella-zoster-, cytomegalo-, human immunodeficiency virus) diseases; bacterial endocarditis also may cause a septic vasculitis which is undistinguishable from PACNS [Berlit, 2009b]. Since the majority of patients with PACNS respond to a therapy with steroids alone it seems reasonable to start with Pred in angiographically diagnosed patients after the exclusion of systemic infection. If relapses occur the diagnosis and the treatment regimen must be reconsidered. With a relapse rate of 25 % and a reduced survival rate a close follow up of suspected PACNS is mandatory [Salvarani *et al.* 2008].

Vasculitis in collagen vascular diseases
Collagen vascular diseases that may lead to immune-complex-related cerebral vasculitis are systemic lupus erythematosus (SLE), rheumatoid arthritis and Sjoegren's syndrome, which is clinically characterized by keratoconjunctivitis sicca and symptomatic xerostomia. The diagnosis of these disorders is made according to the criteria of the American College of Rheumatology. In all collagen vascular diseases thrombotic vasopathies are more frequent than true vasculitides. In SLE in particular, strokes are often caused by a secondary antiphospholipid syndrome. Therefore, lupus anticoagulant and anticardiolipin antibodies should be searched for. Stroke may also be caused by cardiogenic embolism in Libmann–Sacks endocarditis or by thrombotic thrombocytopenic purpura. In both SLE and Sjoegren's syndrome MRI may reveal multifocal white matter lesions in the T2-weighted images in association with the detection of certain antibodies [Berlit, 2007; Sanna *et al.* 2000].

Differential diagnosis of cerebral vasculitis
The progressive bilateral narrowing of the terminal internal carotid artery and the proximal segments of the middle and anterior cerebral arteries of Moyamoya syndrome associated with strokes and headache may be mistaken for cerebral vasculitis. The main pathologic finding in this disease is endothelial thickening due to cellular fibrous tissue which leads to progressive stenosis. There are no inflammatory signs in the vessel wall. As soon as the typical collateral network of small leptomeningeal and transdural vessels occurs, the diagnosis can be made based on DSA findings, but it may be difficult in early stages. If patients present with watershed infarctions, extra–intracranial bypass surgery may

be considered to prevent further infarctions. We perform vessel biopsies routinely during these procedures in order to verify the diagnosis and rule out vasculitis [Krämer *et al.* 2008].

The diagnosis of Sneddon syndrome is based on the presence of fixed deep bluish-red reticular skin lesions on the legs and body (livedo racemosa) in association with strokes. Histologic studies reveal a thrombotic arterial vasculopathy of medium-sized and small arteries. In 35% there is an association with antiphospholipid antibodies. MRI usually reveals rather large ischemic lesions with only few thrombotic vessel occlusions or normal DSA [Berlit, 2004a]. In young stroke patients who present with headache, multiple dissections of the craniocervical arteries should be considered. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is an autosomal dominant disorder that leads to strokes and a progressive vascular encephalopathy in young adults.

Stroke may occur as a serious complication of sympathomimetic drugs including amphetamine, metamphetamine, ephedrine, cocaine, oxymetazoline and phenoxazoline. While intracerebral hemorrhage is the most frequent complication of the use of sympathomimetic agents, ischemic stroke may occur as well. The angiographic pattern in these patients may resemble cerebral vasculitis almost in its entirety.

Other rare conditions sometimes misdiagnosed as cerebral vasculitis include the reversible posterior leucoencephalopathy syndrome, MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), malignant intravascular lymphomatosis, Degos disease, amyloid angiopathy, Fabry's disease, pseudoxanthoma elasticum, lipohyalinosis, and storage diseases. Septic emboli in endocarditis may lead to a septic angiitis. In this situation a blind treatment with immunosuppressive drugs is extremely dangerous.

Conflict of interest statement

None declared.

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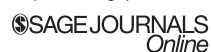
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