Inflammation is associated with cytokine production and acute phase response with associated general symptoms. Accordingly, in almost all primary vasculitic diseases the ESR and CRP are increased (Table 1). Temporal arteritis and the often accompanying polymyalgia rheumatica follow the rule of 50: both the patient and the erythrocyte sedimentation rate (ESR) are usually over 50. However, in primary angitis of the central nervous system ESR and CRP are usually within the reference limits (and the ANCA test is negative).

**Table 1** Laboratory findings of suspected vasculitis in general practice

- ESR and C-reactive protein
- CBC and differential count: anaemia, leucocytosis, eosinophilia and thrombocytosis
- Urine: haematuria, proteinuria, RBC casts
- ANCA: suggest small artery vasculitis
- X-ray paranasal sinuses: opacity/fluid levels
- Chest X-ray: pulmonary infiltrates

Tests are ordered based on the clinical picture and they can also be used to demonstrate the triggering or perpetuating factor in secondary vasculitis and to exclude pseudovasculitis.
Complete blood count with white cell differential is one of the basic laboratory tests to be ordered in suspected vasculitis cases. Primary vasculitis is usually associated with normocytic normochromic anaemia, leucocytosis and thrombocytosis. In contrast, leukopenia is not typical of vasculitis, but can be suggestive of SLE, sepsis or some other severe infection or viral infection, aleukaemic leukaemia, myelodysplasia or various drug toxicities. Thrombocytopenia is not usually seen in primary vasculitis, but is rather suggestive of SLE, infiltration of malignant diseases into the bone marrow, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation or antiphospholipid antibody syndrome. Eosinophilia is part of the Churg-Strauss syndrome, but can also be seen in Wegener’s granulomatosis and rheumatoid vasculitis.

Autoantibody tests are in many places mostly performed in the referral hospital. Selection of the tests is dependent on the clinical symptoms. C-ANCA and proteinases-3 antibodies are strongly suggestive of Wegener’s granulomatosis, whereas p-ANCA with myeloperoxidase specificity rather imply microscopic polyangiitis or Churg-Strauss syndrome. ANCA are seen in many other diseases such as infections, but their reactivity is then usually against something else other than proteinase-3 or myeloperoxidase. Determination of antinuclear antibodies and anti-dsDNA antibodies is recommended when SLE is suspected or has to be excluded. Antiphospholipid antibodies are important when arterial or venous thrombosis or thrombocytopenia are evaluated and are also necessary when catastrophic antiphospholipid antibody syndrome reminiscent of a difficult systemic vasculitis is suspected. Anti-glomerular basement membrane (GBM) antibodies are important when the cause for glomerulonephritis and alveolar bleeding is sought. Goodpasture’s syndrome is characterized by pathogenic anti-GBM autoantibodies. These antibodies react with the noncollagenous 1 (NC1) domain of the α3 chain of basement membrane type IV collagen in glomeruli (glomerulonephritis) and alveoli (alveolar bleeding), where the corresponding autoantigen is relatively exposed. Serological tests for the demonstration of hepatitis B and C can be recommended in polyarteritis nodosa, cryoglobulinaemia, polyarthritis or cutaneous vasculitis. Serum C3 and C4 are often consumed in cryoglobulinaemia, but are usually normal in polyarteritis nodosa, Wegener’s granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome and can increase in infections as they are acute phase reactants.

Routine and microscopic examination of urine demonstrates proteinuria, haematuria and red blood cell casts (renal injury) associated with azotemia in glomerulonephritis. Tubular lesions due to ischaemic nephropathy in polyarteritis nodosa lead to proteinuria. Vasculitis patients may have arthritis, with a mildly inflammatory and sterile synovial fluid. Positive stool occult blood test (gastrointestinal bleeding, less than 150 ml/day may not suffice to cause melaena) hints to bowel involvement in a patient with abdominal pain.

Histopathology forms the basis of definite diagnosis, but because such procedures are invasive, attempts have been made to develop surrogate markers. Glomerulonephritis can be diagnosed if the patient has proteinuria, haematuria and red blood cell casts. Radiography of the paranasal sinuses can demonstrate changes in sinuses (mucosal thickening, fluid level or opacity) in Wegener’s granulomatosis. Chest X-ray can either demonstrate multiple, bilateral and chronic (> 1 month) solid nodules and cavities in Wegener’s granulomatosis (granulomas) and diffuse and non-fixed infiltrates in alveolar capillaritis in Churg-Strauss syndrome and microscopic polyangiitis (inflammatory cell infiltrates). Other surrogate parameters defined in the Chapel Hill nomenclature are specified in Table 2.

Table 2: Surrogate markers in the diagnosis of vasculitis

| Target organ | Surrogate parameter |
|--------------|---------------------|
| Glomerulonephritis | Proteinuria, haematuria and red blood cell casts |
| Arteritis | Angiographic or ultrasound demonstration of aneurysms or stenosis in arteries if clinical signs of vasculitis also present |
| Granulomatous inflammation of the upper respiratory tract | Bloody nasal secretions and/or inflammation in the upper respiratory tract, which last for longer than one month |
| Chronic sinusitis, otitis and/or mastoiditis (X-ray, CT or MRI) |
| Sudden hearing loss without trauma |
| Destruction of the skull bones and/or cartilage |
| Granulomatous inflammation of the lower respiratory tract | Radiological demonstration of inflammation in lower respiratory tract (shadowing or cavitations), which lasts longer than one month |
| Inflammation of pulmonary capillaries | Radiologically diffuse infiltrates, which last for at least one month |
develops an acute onset dyspnoea and haemoptysis. Chest X-rays in Takayasu disease and temporal arteritis may reveal widening of the ascending aorta and irregularities of the descending aorta or even dystrophic calcifications of the diseased tissues. Myocardial involvement may lead to cardiomegaly, congestion and extravasation, but can also be conveniently shown using electrocardiogram, which may demonstrate tissue ischaemia, injury or necrosis, arrhythmias and conduction blocks. Myocardial damage can be shown by using serum measurements of myoglobin, troponin T and CK-MB. Myositis leads to leakage of CK, aldolase and myoglobin into the circulation.

Patients with unstable angina pectoris are urgently referred to hospital. The same principle should naturally apply to progressive and unpredictable vasculitic changes as “unstable vasculitic plaques” can lead to severe vital organ damage and failure of heart, kidneys, bowel, brain, and lungs. Early diagnosis is important in the management of systemic vasculitis. Use of anti-platelet drugs or anticoagulants is difficult in vasculitis, which is associated with a bleeding tendency so that such drugs may be contraindicated in spite of a prothrombotic inflammatory vessel wall condition. Therefore, diagnosis and early treatment are the clinician’s primary concern.

THE THIRD MILESTONE: TESTS IN SPECIALIZED CENTRES

Computed tomography

Computed tomography may demonstrate changes in the paranasal sinuses (mucosal thickening, fluid level and shadowing in Wegener’s granulomatosis) and the lungs (nodules and cavities/granulomas in Wegener’s granulomatosis, inflammatory cell infiltrates in Churg-Strauss syndrome and microscopic polyangiitis, and predominantly peripheral, bilateral ground-glass alveolar infiltrates/alveolar bleeding in any of these) even when standard X-ray pictures appear normal.

Histopathology

Evaluation at a specialized centre should focus on biopsies of involved organs. Selection of targets for biopsies is based on clinical findings, laboratory tests and other objective examinations and clinical risk-benefit ratio. For example, in polyneuropathy patient electromyography (ENMG) can be used to disclose abnormal conduction in the sural or in some other peripheral nerves indicating a favoured site for a nerve biopsy to demonstrate necrotizing arteritis or ischaemic neuropathy. MRI can demonstrate inflammation, oedema or scarring in myositis and can be used to select the muscle biopsy site. Biopsies can demonstrate macrophages, granulomas, necrosis, T lymphocytes and immunoglobulin and complement depositions.

The diagnosis of Takayasu arteritis can rarely be confirmed by histology ante mortem, as it is difficult to obtain biopsies of the target lesions in aorta and its large branches. In contrast, in the other giant cell arteritis (temporal arteritis), temporal artery biopsy demonstrates destruction of the lamina elastica interna, inflammatory cells in the vessel wall and giant cell granulomas. Because these inflammatory changes are patchy, focal and segmental, it is generally recommended that 2–3 cm of temporal artery is taken to avoid false negative result. False negative biopsies still occur, indicating that the decision to treat with glucocorticosteroids is eventually the clinician’s responsibility.

Polyarteritis nodosa is characterized by necrotising inflammation of medium- and small-sized muscular arteries, which may only involve part of the vascular circumference at vessel bifurcations (segmental involvement). Such inflammation weakens the arterial wall in a patchy manner, eventually leading to an aneurysm, thrombosis and/or localized rupture. Such changes may be clinically palpable as pulsating nodules and are histologically characterized by neutrophil-rich infiltrates. Skin, muscle and nerve are helpful biopsy sites and demonstrate in the active phase necrotic (fibrinoid necrosis) and neutrophil-rich (also monocyte/macrophages, lymphocytes and eosinophils are present) arteritis of the medium- and/or small-sized arteries. The vascular lumen may contain a thrombus and the acute inflammatory changes are replaced by fibrous thickening in the long term. Kawasaki disease is diagnosed without histopathological confirmation, but autopsies have disclosed vasculitic coronary artery aneurysms with thrombotic occlusion and myocardial infarction as the cause of death.

In Wegener’s granulomatosis, biopsies taken from nasal mucosa or upper airways may contain so much necrotic tissue, that demonstration of vasculitis can be difficult. Open or thoracoscopic lung biopsies demonstrate vasculitis, necrotizing inflammation and giant cell granulomas, but are more invasive. Focal, segmental and necrotizing rapidly progressive changes lead to proliferation and sclerosis, i.e. to crescentic (= extracapillary proliferation) glomerulonephritis characterized by the absence or paucity of immunoglobulin deposits (= pauci-immune) in AAV. This change is typical for Wegener’s granulomatosis. In Churg-Strauss syndrome and microscopic polyangiitis biopsies are usually obtained from affected nerves (e.g. sural), muscles, skin, lung or kidney. In Churg-Strauss syndrome the typical findings in the...
open or thoracoscopic lung biopsy are small, extravascular, necrotizing granulomas and necrotizing vasculitis involving small arteries, capillaries and venules, coupled with extravasated eosinophils. Glomerulonephritis is rarer and usually milder in Churg-Strauss syndrome and microscopic polyangiitis than in Wegener’s granulomatosis. Pauci-immune, crescentic glomerulonephritis is confirmatory, but not diagnostic, of these disease entities. Granulomatous inflammation caused by microbes should be excluded in Wegener’s granulomatosis and Churg-Strauss syndrome. Histologically microscopic polyangiitis, which spares middle-sized muscular arteries, is a necrotizing, non-granulomatous vasculitis identical to that seen in polyarteritis nodosa.

Leucocytoclastic (necrotizing) vasculitis of the small blood vessels in the skin is characterized by neutrophils, nuclear dust, fibrinoid necrosis of the vessel walls and extravasation of erythrocytes. In Henoch-Schönlein purpura, skin biopsy demonstrates leucocytoclastic vasculitis with IgA and C3 deposits, in the other forms usually IgG and C3 are found. These IgA and C3 deposits can also be found in renal biopsies deposited in mesangium, similar to the findings in IgA nephropathy. If crescent formation develops, the prognosis is more sinister in Henoch-Schönlein purpura.3 In cryoglobulinemias, lymph node (lymphoproliferative disorders), liver (hepatitis C in mixed cryoglobulinaemia), skin (SLE) or labial salivary gland biopsies (Sjögren’s syndrome) may be indicated.

In Goodpasture’s syndrome renal and lung biopsies disclose linear deposits of autoantibodies along the basement membrane.

Angiography and other imaging studies

Lesions in the vascular wall can lead to stenosis, occlusion, aneurysm, dissection, bleeding, thrombosis, embolism, ischaemia, inflammation and oedema. Angiography and Doppler ultrasound examination can demonstrate stenosis, occlusions, aneurysms, thrombosis and bleedings. X-rays, computed tomography and magnetic resonance imaging are suitable for the demonstration of bleeding, lesions, complications and assessment of the extent of the disease. If no good targets for biopsies can be used or found, it is possible to use angiography to demonstrate stenosis and post-stenotic dilations, aortic aneurysms, dissection and microaneurysms.

Echocardiography can disclose aortic valve insufficiency and aortic aneurysms. High-resolution colour Doppler ultrasound offers a useful non-invasive method for the diagnosis and guidance of the site of biopsy in, e.g. temporal arteritis as it typically demonstrates narrowing of the lumen associated with a periluminal halo indicating oedema and inflammatory cell infiltrates. Diagnosis of Takayasu arteritis is usually reached by angiography. Routine angiography exposes the patient to radiation and catheterisation related hazards, but provides accurate information on the size of the vascular lumen and allows measurement of the pressure differentials in the same session. MRI is non-invasive, does not cause radiation load and provides information on the vessel wall. Contrast-enhanced CT can be used to show stenosis, post-stenotic dilatation and changes in the contours of the vessel wall. Gadolinium-enhanced magnetic resonance angiography (MRA) is useful for the evaluation of the size of the lumen of the large blood vessels and the thickness of their wall.4–6 Disease activity assessment using these methods is difficult. In one study, 44% of the patients considered clinically to have a quiescent disease, disclosed signs of an ongoing active vasculitic process in samples obtained at bypass surgery.7 Although imaging of the vessel wall oedema using MRI is a relatively safe and non-invasive method to assess the vascular pathology, it does not actually seem to be a very accurate indicator of ongoing disease activity.4 Positron emission tomography (PET), which is able to demonstrate metabolic/inflammatory activity, looks more promising for disease activity assessment,8 but access to PET is limited.

In Kawasaki disease, an echocardiography should always be performed to check for coronary artery ectasias and/or aneurysms. Doppler echo can demonstrate arterial narrowing and dilations in classical polyarteritis nodosa. Angiography of the mesenteric, splanchic or renal arteries is used when arteritis of the middle-sized arteries is suspected and historical diagnosis has not been obtained. Polyarteritis nodosa has fusiform or saccular microaneurysms, smooth tapered occlusions and thrombosis in 60–90% of cases. Aneurysms are more likely to develop with time and are not always found in the early stages of the disease. Microaneurysms of internal organs are suggestive but not diagnostic of polyarteritis nodosa, as they can also be found in other diseases affecting slightly smaller arteries, for example in Wegener’s granulomatosis and Churg-Strauss syndrome, as well as in non-vasculitic conditions, such as atrial myxoma and in infective endocarditis. In primary angiitis of the central nervous system, the diagnostic work up usually begins with magnetic resonance imaging of the brain, which is usually abnormal, and by examination of the cerebrospinal fluid, which usually demonstrates inflammatory changes in the granulomatous disease. Diagnosis of the benign form of the disease is based on angiography, and of granulomatous disease on biopsy and associated inflammatory changes in the cerebrospinal fluid. Angiography can be used in Kawasaki disease and arteritis affecting coronary arteries. In Buerger’s disease angiography of the extremities discloses non-atherosclerotic occlusions,
which, in longstanding disease, are often surrounded by
corkscrew like collaterals. Angiography is particularly use-
ful in the diagnosis of vasculitides affecting the aorta and
large and medium-sized arteries, but has no place in the
diagnosis of small vessel vasculitis.

REFERENCES

1. Savige J, Pollock W, Trevisin M. What do antineutrophil cyto-
plasmic antibodies (ANCA) tell us? Best Practice Res Clin
Rheumatol 2005; 19: 263–76.
2. Pipitone N, Boiardi L, Salvarani C. Are steroids alone suffi-
cient for the treatment of giant cell arteritis? Best Practice
Res Clin Rheumatol 2005; 19: 277–92.
3. Bhuyan UN, Tiwari SC, Malaviya AN, Srivastava RN, Dash
SC, Malhotra KK. Immunopathology and prognosis in
Henoch-Schonlein glomerulonephritis. Ind J Med Res 1986;
83: 33–40.
4. Tso E, Flamm SD, White RD, Schwartzman PR, Mascha E,
Hoffman GS. Takayasu’s arteritis: utility and limitations of
magnetic resonance tomography in diagnosis and treatment.
Arthritis Rheum 2002; 46: 1634–42.
5. Kissin EU, Merkel PA. Diagnostic imaging in Takayasu
arteritis. Curr Opin Rheumatol 2003; 16: 31–7.
6. Schmidt WA, Gromnica-Ihle E. What is the best approach to
diagnosing large-vessel vasculitis? Best Practice Res Clin
Rheumatol 2005; 19: 223–42.
7. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS,
Rottem M, Hoffman GS. Takayasu arteritis. Ann Intern Med
1994; 120: 919–29.
8. de Leeuw K, Bijl M, Jager PL. Additional value of positron
emission tomography in diagnosis and follow-up of patients
with large vessel vasculitides. Clin Exp Rheumatol 2004; 22
(6 Suppl 36): S21–6.

Diagnosis of intracranial vasculitis: a multi-disciplinary approach

Intracranial vasculitis, or primary angiitis of the central nerv-
ous system (PACNS), is an uncommon, often fatal disorder
that frequently responds to aggressive immunosuppressive
therapy. Magnetic resonance imaging (MRI), cerebral angiog-
raphy, and brain biopsy are diagnostic modalities that vary
in invasiveness and diagnostic accuracy. The purpose of this
study was to determine whether certain clinical or radiologic
features were predictive of a diagnostic biopsy. Thirty consec-
utive patients undergoing brain biopsy to “rule out vasculi-
tis” were studied. Nine patients demonstrated granulomatous
or lymphocytic vasculitis, 1 had lymphocytic vasculitis and
encephalitis secondary to arbovirus infection, 5 had thick-
ened vessels consistent with hypertensive changes, 5 had
amyloid angioapathy and/or changes of Alzheimer disease,
5 demonstrated no pathologic abnormalities, and 1 each had
acute infarct, vascular malformation, aneurysm, acellular fib-
rinoid necrosis, and demyelination. The spectrum of MRI and
angiographic changes associated with PACNS were nonspe-
cific, overlapping extensively with changes of chronic hyper-
tension and amyloid deposition. The predictive values of
brain biopsy (90–100%) were significantly higher than those
of angiography (37–50%) or MRI (43–72%). In this study,
morbidity associated with aggressive immunosuppression
was significantly greater than that associated with cerebral
angiography or brain biopsy. Thus, wedge biopsy of cortical
and leptomeningeal tissues is central to the multi-disciplinary
approach to a patient with clinical suspicion of PACNS.

Source: Chu CT, Gray L, Goldstein LB, Hulette CM.
J Neuropathol Exp Neurol 1998; 57: 30–8.