Review

Diagnosis and assessment of systemic vasculitis

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Received on August 31, 2002; accepted on September 4, 2002.

Clin Exp Rheumatol 2002; 20: 854-862

Key words: Vasculitis, classification, assessment, diagnosis.

ABSTRACT

The diagnosis of systemic vasculitis requires clinical evidence with appropriate symptoms and physical signs, supported by histological or radiological confirmation. Earlier recognition of these diseases has been facilitated by a greater awareness of their incidence, and also by the more widespread introduction of the anti-neutrophil cytoplasmic antibody (ANCA) test. Early diagnosis provides a greater potential for effective intervention in the course of disease and this may limit subsequent damage. However, an early diagnosis poses the more difficult challenge in the classification of the vasculitides, since traditional classification systems have depended on the presence of well-established manifestations of the disease. The accurate assessment of disease activity and damage in vasculitis has become necessary as a result of significant improvements in survival with the use of chemotherapy. The disease course however is frequently characterised by relapse as well as the scars of irreversible organ damage from disease and drug toxicity. Clinical methods of assessment are simple to apply, reliable and often more effective than any current laboratory test in evaluating the effects of therapy and determining changes in therapy. The increasing use of surrogate clinical measures of disease should provide a greater opportunity to establish the effectiveness of existing and novel therapies in the management of these complex diseases.

Introduction

The systemic vasculitides are an uncommon group of multi system diseases (incidence 42 cases/million/annum) (1). The diagnosis of vasculitis is usually established in patients presenting with clinical features of multiple organ involvement, and confirmed by histological or occasionally radiological evidence of characteristic vessel involvement. Serological markers of vasculitis such as the presence of ANCA have significantly improved our awareness of some of the primary vasculitides and influenced the increased reporting of new cases per annum (2, 3). Classification of vasculitis serves to improve our knowledge of the natural history of these diseases but cannot be used to establish the diagnosis (4).

The use of cytotoxic drugs, especially cyclophosphamide, has significantly reduced the mortality rate in vasculitis (5, 6) but unfortunately patients suffer significant morbidity. Treatment-related toxicity (7) and chronic scarring from previous disease are common features in the long-term and may have a major impact on the quality of life in those patients who survive their initial illness (8,9). Relapses are frequent (6, 10) and we should now regard the systemic vasculitides as chronic diseases.

Diagnosis and classification of systemic vasculitis

Vasculitis may be primary, or secondary to underlying connective tissue disease, malignancy, infection or drugs. In primary vasculitis several well established clinical syndromes have been described [Table I (11-30)]. However, in practice, overlap is common and the distinction between disease entities becomes blurred.

Establishing a diagnosis of vasculitis requires a thorough history and physical examination as many of the syndromes are based on clinical rather than laboratory features. The presence of typical features of vasculitis in multiple systems is very important [Table II (31)]. Few diseases can cause such a widespread pattern of involvement. The more organ systems involved, the narrower the differential diagnosis becomes. Supporting evidence may be sought from raised inflammatory markers and serological tests such as

Table I. Primary vasculitis.

	Epidemiology	Symptoms and signs	Investigations	Treatment
Giant cell (temporal) arteritis (LV)	Elderly, rare < 50 years Annual UK incidence 13/million adults or 42/million adults > 60 years (11)	Severe headache, scalp tenderness, visual disturbance, jaw claudication; often associated with polymyalgia	Elevated ESR, temporal artery biopsy - although skip lesions occur; angiography for major vessel involvement	Corticosteroids. Relapse rates vary from 30-80% during corticosteroid tapering over 1 to 4 years of follow up (12).The role of methotrexate as an adjunctive therapy remains unsettled (13, 14)
Takayasu's arteritis (LV)	Young, usually < 50 years Female predominance Eastern countries esp. Japanese Annual UK incidence 0.1/million (15)	Chronic ischaemia, new loss of pulses, bruits	Angiography shows vessel narrowing with post-stenotic dilatation	Corticosteroids 5 – 10 year survival 80 – 90%. 47% permanent disability (16)
Polyarteritis nodosa (MV)	Adults Annual UK incidence 0-4.6/million (15)	Multisystem involvement - muscle, nerve, gut and skin but not usually renal involvement unless infarction occurs	Hepatitis B virus (HBV) positive in some cases Biopsy; Angiography shows aneurysms	Corticosteroids combined with either interferon alpha (HBV +ve) or cyclophosphamide (HBV -ve) Mortality 23% (non HBV PAN) - 33 % (HBV related PAN); relapse 8% (HBV related PAN) - 20% (non HBV PAN) (17-20)
Kawasaki disease (Mucocutaneous lymph node syndrome) (MV)	Children (peak incidence at 1 year), rarely adults Endemic and epidemic forms occur worldwide. Seasonal variation? infectious aetiology Annual UK incidence 34/million children < 5 years (21) Annual Japanese incidence 900/million children < 5 years (22)	Persistent fever; conjunctivitis; erythema of lips, buccal mucosa and tongue; acute non-purulent cervical lymphadenopathy; polymorphous exanthema; erythema of palms and soles. Coronary arteries often involved Diagnosis based on 5/6 clinical criteria or 4/6 plus coronary artery dilatation on echocardiography	Mucocutaneous or lymph node biopsy performed if diagnostic uncertainty	Aspirin and intravenous immunoglobulin (23). IVIG has decreased the incidence of giant aneurysms frequently complicated by thromboses, stenosis or total occulusion (24). Coronary artery lesions in 15-25% of untreated patients but <10% of those receiving IVIG (24)
*Wegener's granulomatosis (SV)	Adults mainly, can occur in children Annual UK incidence 8.5/million (15)	Upper and lower airways, often renal involvement; may be limited to lung or ear, nose and throat	Biopsy - granulomas in airways, focal segmental necrotising glomerulonephritis (FSNGN) on renal biopsy, usually ANCA positive	Localised upper airway disease: prednisolone and methotrexate (25); cotrimoxazole or mupirocin for eradication of nasal *Staphylococcus* (26). Systemic disease: prednisolone and cyclophosphamide (27); plasmapheresis has been used but the results are controversial and there is a randomised controlled European trial (MEPEX) recently completed but not yet reported
*Churg-Strauss syndrome (SV)	Adults mainly, can occur in children Annual UK incidence 2.4/million (15)	Respiratory tract (asthma, allergic rhinitis, pulmonary infiltrates), mononeuritis multiplex; cardiac involvement is serious	Eosinophilia, may be ANCA positive (usually pANCA)	Corticosteroids; cyclophosphamide for serious disease (cardiac) Mortality low but high relapse rate (17, 19)
*Microscopic polyangiitis (SV)	Adults mainly, can occur in children Annual UK incidence 2.4/million (15)	Haematuria, pulmonary haemorrhage	Renal biopsy – FSNGN, may be ANCA positive (usually pANCA)	Corticosteroids and cyclophosphamide +/- plasmapheresis Mortality 10-40%; relapse 20% (10, 27)
Henoch-Schonlein purpura (SV)	Children mainly, can occur in adults Annual UK incidence 1.2/million adults (15)	Purpuric rash, flitting arthritis, abdominal pain +/- rectal bleeding or haematuria	Skin biopsy or biopsy of GI tract - IgA-dominant immune deposits	Self-limiting in childhood; adults more indolent course – steroids for arthralgia and rash; optimal treatment for HSP-associated gastrointestinal and renal involvement has not yet been determined but corticosteroids favoured for abdominal pain and immunosuppressive therapy for HSP nephritis (28)
Cutaneous leucoytoclastic vasculitis (SV)	Adults and children	Isolated to the skin	Skin biopsy; positive ANCA may indicate likelihood to progress to systemic disease	Symptomatic treatment with antihistamines; colchicine useful in some patients (29); corticosteroids for resistant cases
Essential mixed cryoglobulinaemia** (SV)	Adults mainly, can occur in children Annual UK incidence 1.2/million (15)	Purpura, arthralgia, urticaria, ulcers, renal involvement	Type II cryoglobulinaemia, strong association with hepatitis C virus (HCV)	Antiviral therapy + corticosteroids/ plasmapheresis (30)
Unclassified	Annual UK incidence 4.8/million (15)	See Table 2	As indicated by organ system(s) involved	As indicated by organ system(s) involved

* These diseases are increasingly grouped together as ANCA-associated systemic vasculitis
** Some may consider this a secondary vasculitis
Predominant vessel size: large vessel (LV), medium vessel (MV), small vessel (SV)
The size of vessel involvement indicates the predominant type of vessel involved but does not exclude other sizes of vessels being involved. For example in small vessel vasculitis affecting the kidney, it is not uncommon for medium vessel disease also to coexist and occasionally for large vessel disease to be present.

Table II. Typical symptoms and signs of systemic vasculitis.*

Systemic	Malaise, myalgia, arthralgia/arthritis, headache, fever, weight loss
Cutaneous	Infarct, purpura, ulcer, gangrene, other skin vasculitis
Mucous membranes/eyes	Oral ulcers, genital ulcers, proptosis, conjunctivits, episcleritis, visual disturbance, uveitis, retinal exudates/haemorrhages
Ear, nose and throat	Nasal obstruction, bloody nasal discharge, crusting, sinus involvement, new deafness, hoarseness/stridor, subglottic stenosis
Respiratory	Persistent cough, dyspnoea, wheeze, haemoptysis, pulmonary haemorrhage, nodules, cavities, infiltrates, pleurisy, pleural effusion, respiratory failure
Cardiovascular	Bruits, new loss of pulses +/- threatened loss of limb, aortic incompetence, pericardial pain/rub, ischaemic cardiac pain, congestive cardiac failure
Gastrointestinal	Severe abdominal pain, bloody diarrhoea, intestinal perforation/infarct, acute pancreatitis
Renal	Hypertension > 95mmHg diastloic, proteinuria > 0.2g/24h, haematuria > 10 rbc/ml, renal impairment/failure, rise in creatinine > 30% or fall in creatinine clearance > 25%
Neurological	Organic confusion/dementia, seizures (not hypertensive), stroke, cord lesion, sensory peripheral neuropathy, cranial nerve palsy, motor mononeuritis multiplex

*The list is of common features reported in a variety of forms of vasculitis. It is by definition not completely comprehensive for every case but does provide a useful checklist of items that may be abnormal in patients with systemic vasculitis – adapted from BVAS (31).

ANCA. It is usually necessary to confirm the diagnosis by histology of the affected tissue if accessible or by imaging with angiographic techniques.

Classification criteria are useful to confirm that a group of patients with a clinical diagnosis have a similar or identical condition. However, in order to discriminate between patients with/without a specific disease, *diagnostic* criteria are required. There are currently no validated diagnostic criteria for primary systemic vasculitis. In practice classification criteria and consensus definitions are often misapplied and as such, they perform poorly (32). They do not include the full spectrum of manifestations of a disease and are therefore not appropriate to use in the diagnosis of the individual patient (33). Classification of vasculitis allows the study of the pathophysiology of vasculitis and the effects of treatment in epidemiological and therapeutic studies by forming a basis for comparing other patient populations involved in studies at different times or in different settings. Classification systems are useful if we are to produce meaningful outcomes from treatment trials among patients with similar disease spectrums but often are too restrictive to be used in a routine clinical setting. Diagnostic criteria determine the combinations of findings that need to be present in order to be certain that a particular disease is present. Features that are present in related conditions may be included. This difference between classification and diagnostic criteria is often misunderstood.

There is no universally accepted classification system for vasculitis, although many different systems have been suggested based on clinical and histopathological features. The size of the predominant vessels involved has formed the basis for most of the recent classifications. The American College of Rheumatology (ACR) classification criteria (1990) (33) and definitions based on a consensus conference at Chapel Hill in 1993 (CHCC) (4) are the most commonly used sets of agreed classification criteria and definitions for vasculitis in current practice and will be discussed further. Neither the CHCC definitions nor the ACR classification criteria are perfect and therefore many groups use both as classification systems when discussing the results of studies relating to patients with systemic vasculitis. The ACR classification criteria were developed primarily to discriminate between patients who had different forms of systemic vasculitis in the setting of patients who had a known diagnosis of vasculitis. This was predominately in order to carry out clinical trials of patients with vasculitis and the criteria were not intended for use in a general clinical setting. The ACR classification criteria (33) were based on 678 patients with primary vasculitis. The ACR subcommittee on classification of vasculitis selected, by a nominal group process, 7 entities to study: Polyarteritis nodosa (PAN), Churg-Strauss syndrome (CSS), Wegener's granulomatosis (WG), hypersensitivity vasculitis (HSV), Henoch-Schonlein purpura (HSP), giant cell (temporal) arteritis (GCA) and Takayasu's arteritis as well as a group of unspecified vasculitides. No criteria or definitions for the diagnosis of distinct vasculitides were proposed before the study and the decision as to which specific type of vasculitis the patient had was made by whatever means were necessary in the judgement of the submitting Rheumatologist (34). The criteria were not tested against control cases (i.e. patients without vasculitis), either in the normal population or against patients with other rheumatological or multisystem illness. They were used as a method of *differential diagnosis* (although designed for *classification*) in patients in whom a diagnosis of vasculitis had already been made. Although only 7 vasculitis categories were proposed, patients were submitted from 48 cen-

tres under approximately 37 different diagnostic titles. The large number of diagnostic titles that were used reflects some of the problems with the nomenclature of vasculitis and this issue was later to be addressed by the CHCC as discussed below. Patients with Kawasaki disease and those with vasculitis secondary to a connective tissue disease (including rheumatoid arthritis (RA)) were excluded but reasons for this are not explained. HSV was included as a defined entity but this is no longer thought to be the case. One hundred and twenty-nine patients with unspecified vasculitis were included in the disease categories but not further analysed. A notable feature of the ACR classification is that they allowed for the fact that not all patients would have undergone histological confirmation of the diagnosis by biopsy, which makes the classification more applicable to use in clinical trials. Another strength of the ACR criteria were the large number of patients included and the inclusion of data from multiple centres. Sensitivity ranged from 71.0% for HSV to 93.5% for GCA and specificity ranged from 83.9% for HSV to 99.7% for CSS.

The CHCC aim was to construct a standardised nomenclature system and hence 'definitions' for common forms of systemic vasculitis. As for the ACR classification criteria, the CHCC definitions were based on histopathological features and clinical symptoms and signs (4). They were arranged predominantly according to vessel size into 10 entities including Kawasaki disease, microscopic polyangiitis (MPA), essential cryoglobulinaemic vasculitis (ECV) and cutaneous leukocytoclastic angiitis (CLA); none of these had been included in the ACR criteria. HSV was not proposed as a separate entity and unclassified vasculitis was not included. However, their table of names and *definitions* of the vasculitides was similar to previously published *classification* criteria and despite the authors best intentions they have often been used in this manner since. Their statement that medium-sized vessel vasculitides such as Kawasaki disease and PAN do not involve small vessels has been contended by Lie (35) and the term 'dominant vessel involved' may be more practical (1). The main drawback of the CHCC definitions are their reliance on histological features which makes them of limited value in routine clinical practice (36) when biopsy material may not be available or may be inconclusive in a significant proportion of cases. As the ACR criteria did not include MPA, WG is over-classified whereas in the CHCC, MPA is probably over-represented at the expense of PAN. The issue of limited forms of WG is not tackled by the CHCC.

The contribution of ANCA status to the diagnosis is not included in either of these systems, since in the case of the ACR criteria, the ANCA test was described only after data had been collected from many patients. In any case ANCA is not present in patients with large vessel vasculitis (37) or medium vessel vasculitis. Furthermore, it has no clinical relevance if it is present in secondary forms of vasculitis, when in most instances ANCA is of non-specific variety, neither directed against MPO nor against PR3 (38). A modified approach to classification has been proposed (1) in which aspects of pathology, aetiology, approaches to treatment and ANCA status are all included. Scott and Watts (1) suggested that WG, CSS and MPA should be grouped separately from HSP, ECV and CLA because the former often involve small arteries, are most commonly associated with ANCA and with a high risk of glomerulonephritis and respond best to cyclophosphamide. The aetiology of HSP and ECV is thought to be related to immune complex deposition and hence they are classified separately. Treatment options can also be used as a discriminating feature for other vasculitides. PAN associated with hepatitis B can be treated with antiviral therapy in some cases (18) and Kawasaki disease may be treated with intravenous immunoglobulin (23) whereas WG and related disorders frequently require the use of steroids +/- cyclophosphamide (27). The evidence base for current treatment of systemic vasculitis was recently reviewed by Luqmani (39).

Secondary vasculitis

Vasculitis may be associated with RA, systemic lupus erythematosus (SLE) or other connective tissue disorders or occur in response to infection (e.g. HBV, HCV and HIV), malignancy or drugs [Table III (15, 40-46)]. The importance of recognising secondary vasculitis is in order that the underlying cause can be treated in the first instance where appropriate, although the development of vasculitis may alter the treatment regime considerably e.g. in RA. Several important non-vasculitic disorders may mimic systemic vasculitis and these need to be considered in the differential diagnosis [Table IV (47)].

Assessment of vasculitis

As the prognosis for patients with systemic vasculitis has improved following the introduction of immunosuppressive therapy (6, 48), the aim of treatment has broadened to include not only increased survival but also reduction in disease and treatment-related morbidity. Patient assessment should therefore include not only an assessment of disease activity, but also the damage that may have accrued as a consequence of the disease or its treatment, and the patient's functional status.

At presentation, patients require a clinical evaluation, looking for evidence of active vasculitis, or damage which may be attributable to previous episodes of vasculitis. This should include a full assessment of the peripheral vasculature, otoscopy, fundoscopy, examination of the skin and nail beds, and dipstick testing of urine as well as cardiorespiratory, abdominal, neurological and locomotor examination. Blood should be taken for estimation of renal and liver function and haematology as well as acute phase reactants. Samples should also be sent for appropriate diagnostic investigations (see above). Imaging and further assessment of organ function will depend on the findings on initial assessment but a chest X-ray is an important investigation irrespective of symptoms and signs. Neoplastic disease can be associated with extrapulmonary vasculitis and the presence of pulmonary nodulosis or

Table III. Secondary vasculitis.

	Epidemiology	Symptoms and signs	Treatment
Rheumatoid	Annual UK incidence 12.5/million (15)	Mononeuritis multiplex or acute peripheral neuropathy, peripheral gangrene, deep cutaneous ulcers, active extra-articular disease if associated with typical digital infarcts (40)	Corticosteroids and immunosuppressive drugs (40)
Systemic lupus erythematosus	Annual UK incidence 3.6/million (15)	Cutaneous Visceral – mononeuritis multiplex, digital necrosis, large vessel vasculitis Visceral vasculitis associated with increased mortality when controlled for age of onset and nephropathy (41)	Corticosteroids and immunosuppressive drugs (41)
Behçet's syndrome	Prevalence varies widely between populations (~ 1:1000 in Turkey, 1:10,000 in Japan and 1:300,000 in Northern Europe) (42)	Relapsing aphthous mouth ulcers, genital ulcers and uveitis form the typical clinical triad; may also involve musculoskeletal, gastrointestinal, cardiovascular, respiratory and central nervous systems. Immune-mediated; small, medium and large vessels affected	Corticosteroids and immunosuppressive drugs (43)
Buerger's disease		Intermittent claudication, rest pain, ischaemic ulcers, thrombophlebitis, Raynaud's phenomenon, abnormal pulses, sensory abnormalities (44)	Stop smoking/use of tobacco Treatment of ischaemic ulcers Trial of calcium channel blockers Prostacyclin Sympathectomy Amputation (rarely necessary if patient stops smoking)
Other connective tissue diseases		Clinical signs of vasculitis observed in 18% polymyositis and 39% dermatomyositis cases in a series of 50 patients (45)	Corticosteroids and immunosuppressive drugs
		Primary Sjögren's syndrome: cutaneous and CNS vasculitis most frequent Visceral involvement may occur (renal, lung, liver, pancreas, bowel) (46)	Cutaneous : low dose corticosteroids, hydroxychloroquine, dapsone Visceral / CNS : high dose corticosteroids + immunosuppressive drugs
Miscellaneous	Annual UK incidence 1.2/million for infection and 0.8/million for malignancy (15)	Infection, malignancy, drug history	Treat or remove underlying cause

infiltrates, which may be asymptomatic in vasculitis, can be helpful in making a diagnosis. In addition, it is important to determine whether there is evidence of previously undiagnosed infection such as tuberculosis as many patients with vasculitis are offered immunosuppressive treatment.

In view of the multisystem nature of systemic vasculitis, serial estimation of disease activity/damage should include assessment of each organ system. Several clinical tools are now available for this purpose [Tables V-VII (31, 49-54)]. The Birmingham Vasculitis Activity Score (BVAS) (31) uses physician assessment to attribute clinical features to the presence of vasculitis. Originally, each of the 59 BVAS items were grouped into 9 organ-based systems and weighted according to the perceived severity of organ involvement e.g. for ocular involvement retinal haemorrhage scored 6 points whereas conjunctivitis scored only 1 point. Subsequent modifications (55) have simplified the scoring system allowing the physician to distinguish clinical features attributable to vasculitis which are worsening from those which are present but stable. Other clinical measures of disease activity (49-51) share with BVAS the potential drawback of relying on the physician to correctly attribute clinical features to vasculitis rather than e.g. infection which can mimic vasculitis very closely. In addition, the Groningen Index (49) and the Disease Extent Index (which measures damage as well as disease activity) (50) are only applicable to WG. Nevertheless in the absence of a gold standard for assessing disease activity, clinical assessments have the advantage of reflecting real life clinical scenarios. BVAS has also been shown to correlate closely with other clinical and laboratory estimates of disease activity (27, 56). Unlike these indices however, which do not provide any prognostic information, Guillevin *et al.* (54) demonstrated a linear relationship between five-year mortality and the presence of one or more of five factors [proteinuria >1 g/day, renal insufficiency, cardiomyopathy, CNS involvement and involvement of the GI tract (bleeding, perforation, infarction and/or pancreatitis)] in a prospective study of 342 patients with either PAN or CSS. Consideration of these factors may therefore allow clinicians to tailor therapy more accurately in these diseases (17).

Damage is an indicator of disease severity in vasculitis. The Systemic Necrotising Vasculitis Damage Index (SNVDI) is derived from the ACR SLE Damage Index and records radiological and laboratory as well as clinical variables associated with end-organ damage occurring as a result of the disease or its treatment (52). Its use thus far has been restricted to PAN/CSS. The Vasculitis Damage Index (53) is

Table IV. Differential diagnosis of systemic vasculitis (47).

Pseudovasculitis (vasculitis-like syndromes)
Embolism from atrial myxoma, cholesterol emboli
Drug induced vasospasm (methysergide, ergot derivatives)
Thrombosis (APL syndrome, sickle cell disease, TTP)
Vessel wall pathology (calciphylaxis, amyloidosis)

Table V. Assessment of disease activity.

Assessment tool	Scoring system	No. items recorded	Comments	Reference
Birmingham Vasculitis Activity Score (BVAS)	Physician and laboratory assessment of 9 organ systems.	59	Applicable to systemic vasculitis.	(31)
Groningen Index	Physician, laboratory and histological assessment of 9 organ systems.	35	Only applicable to WG.	(49)
Disease Extent Index (DEI)	Physician and radiological assessment. Assesses damage as well as activity.	17	Only applicable to WG.	(50)
Vasculitis Activity Index (VAI)	Physician assessment of 9 organ systems on VAS plus mean of 3 indirect measures of disease activity (ESR, fatigue, fever).	12	Correlates with physician global assessment.	(51)

Table VI. Assessment of damage.

Assessment tool	Scoring system	No. items recorded	Comments	Reference
Systemic Necrotising Vasculitis Damage Index (SNVDI)	Physician and radiological assessment of 12 organ systems.	34	Only applicable to CSS/ PAN.	(52)
Vasculitis Damage Index (VDI)	Physician assessment of 11 organ systems.	64	Applicable to systemic vasculitis.	(53)

Table VII. Assessment of severity.

Assessment tool	Scoring system	Comments	Reference
Five Factor Score (5FS)	Clinical and laboratory assessment of organ involvement.	Applicable at initial assessment. Provides prognostic information.	(54)

applicable to any of the systemic vasculitides and records 64 clinical items grouped into 11 organ-based systems. Items are recorded if they have been present for at least 3 months to distinguish damage from active disease and each item is scored as being present or absent. Acute irreversible items such as myocardial infarction are scored 3 months after the event to maintain uniformity. The index is cumulative and can only remain stable or increase. Damage can be recorded separately from active disease, a distinction that is important not only in therapeutic decision making, but also as an indicator of prognosis (8, 57).

As well as recording disease activity and damage, it is also important to assess the consequences this has for the individual in terms of function. Abu-Shakra *et al.* (52) used the Health Assessment Questionnaire (HAQ) to measure function in PAN/CSS and found higher pain and disability indices in PAN. The HAQ however was devised to assess function in RA (58) and in the absence of a functional index specific for vasculitis, it may be preferable to use a more generic measure such as the Short Form 36 (SF-36) (59). Along with BVAS and VDI, SF-36 has been incorporated into the VITAL assessment of vasculitis (9, 60) which gives a global picture of disease activity, damage, and subsequent consequences for function.

Basic biochemical and haematological parameters and measurement of the acute phase response may help in differentiating active disease from irreversible damage. Sophisticated indices of endothelial cell (EC) perturbation such as thrombomodulin (TM) or von Willebrand factor (vWF) may give additional information beyond that provided by acute phase reactants, but markers of EC perturbation are currently of value as research tools only. Serial measurements of TM, a transmembrane glycoprotein of endothelial cells which is released in response to EC damage, have suggested a close correlation between serum levels and disease activity as judged by BVAS (56) and other forms of clinical assessment (61). Raised plasma levels of vWF have also been demonstrated in various forms of vasculitis (62-67) but it is uncertain whether elevated levels represent active disease or irreversible damage. Similarly, raised plasma levels of adhesion molecules such as soluble intercelluar adhesion molecule-1 (sICAM-1) and E-selectin have been shown in vasculitis (68, 69) but may reflect damage as well as active disease. Serum hyaluronan (70) and serum neopterin (71), a compound secreted by macrophages following stimulation by interferon-γ have also been shown to be raised in a small number of patients with systemic vasculitis. The question of whether serum levels of ANCA can be used to monitor disease activity and predict disease relapse in ANCA-associated vasculitis remains open (72-75). Recently it has been suggested that proteinase 3 expression on circulating neutrophils rather than ANCA levels may be a more accurate reflection of disease

activity in WG (76). Extra-renal disease, granulomata and disease relapse may also be more common in patients with ANCA-positive vasculitis who have antibodies to proteinase 3, compared to those with anti-myeloperoxidase antibodies (77).

Differentiating active vasculitis from infection

There is a close relationship between infection and vasculitis disease activity. Infection may cause vasculitis *de novo* or exacerbate pre-existing disease, particularly in patients on immunosuppressive drugs. *Staphylococcal* superantigen enterotoxins have been implicated in both the aetiology of Kawasaki disease (24) and as a risk factor for disease relapse in Wegener's granulomatosis (78). It may be difficult on clinical grounds to exclude infection in a patient with worsening vasculitis in whom typical pointers such as pyrexia or rigors may be masked by immunosuppressive drugs. Similarly, laboratory indicators of infection such as neutrophilia or elevated C-reactive protein may be absent or attributed to active vasculitis. Serum levels of procalcitonin, if available, may be helpful in differentiating active disease from infection (79).

If a patient who is known to have vasculitis becomes unwell, a fresh microbiological assessment of appropriate samples should be sent for culture and if possible, these results obtained before attributing the deterioration to vasculitis. It may be necessary however to prescribe empirical antibiotic therapy along with more aggressive immunosuppression while waiting for culture results. Chronic nasal carriage of *Staphylococcus aureus* may be an important risk factor for relapse in WG (26) and at present there is a randomised control trial to observe whether the eradication of asymptomatic nasal *Staphylococcus* infection in WG by topical mupirocin therapy will successfully reduce the risk of further relapse (80).

Conclusions/Summary

Diagnosis of vasculitis continues to depend on clinical expertise usually supported by characteristic histological evidence. There are no diagnostic criteria for systemic vasculitis, and perhaps it would be an appropriate time to consider their development. Classification systems for vasculitis are helpful but limited in scope. Our current therapies have transformed the systemic vasculitides from life-threatening conditions to chronic relapsing diseases with considerable morbidity. Disease assessment allows the opportunity to improve therapy by helping us to differentiate activity from damage, to perform properly controlled long-term studies in a multi-centre setting and to assist the clinician in the management of individual conditions or patients. The most effective and more importantly the least toxic regimens for the management of vasculitis have yet to be established. However, as our understanding of aetiology and disease mechanisms improves it may be possible to target immunotherapy more precisely in the management of these complex diseases.

Acknowledgement

Mrs Anne Houghton for her secretarial support.

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