Assessment of disease activity in systemic vasculitis

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Summary

The systemic vasculitides are a group of inflammatory disorders characterised by relapses and remission. Before the introduction of immunosuppressive drugs, mortality was unacceptably high. Immunosuppressive therapy has had a therapeutic impact, but at the cost of increased risk of infection and other adverse effects. Differentiating infection from active disease can be difficult, and the inappropriate prescription of immunosuppressive drugs can be fatal. Hence disease indices which can aid physicians to identify the active phase of disease and enable early treatment, will be valuable in the management of this group of disorders.

Keywords: systemic vasculitides

Systemic vasculitis describes a variety of overlapping multisystem disorders, characterised by inflammation and necrosis of blood vessels.¹ The prognosis for survival in this group of disorders has been improved dramatically by immunosuppressive therapy; in Wegener's granulomatosis, 80% of patients now survive for more than five years compared with earlier mortality rates of greater than 80% at two years.²⁻⁵ However, survival may be complicated by frequent relapses and morbidity arising directly from the disease and treatment-related complications are a matter of concern.²⁻⁴ Minor relapses or insidious progression of disease are often difficult to assess. Further, distinguishing infection from active disease can be difficult, and misdiagnosis resulting in an escalation of immunosuppressive treatment can lead to a fatal outcome if there is underlying infection. This emphasises the need for accurate disease assessment. In this review, we discuss ways of monitoring disease activity.

Clinical features and disease activity indices

Constitutional features such as weight loss, malaise, anorexia and fever are often present in the active phase of the disease. Other features can include a rash, arthralgia, myalgia and conjunctivitis. However, these symptoms are non-specific and can be found in a range of disorders. The presence of systemic symptoms together with evidence of dysfunction of major organs, such as the lungs or the kidneys, should lead one to suspect a multi-organ disorder. Similarly, re-emergence of these symptoms in patients with an established diagnosis of vasculitis should alert physicians to the possibility of a relapse and appropriate investigations should be instigated.

A number of disease activity indices have been developed to aid objective measurement of disease activity, damage, response to treatment and functional impairment. The Birmingham Vasculitis Activity Score (BVAS) comprises a series of descriptive clinical statements devised to compare disease activity in vasculitis.⁶ Luqmani *et al* found that those patients who subsequently died tended to have a higher BVAS score.⁶ Thus the actual score may provide prognostic data on patient survival, and may also allow physicians to identify those patients who are at risk of aggressive disease and merit closer follow-up. The BVAS provides a measurement of disease activity but does not include data on chronic damage arising from the disease or treatment, nor on the effects of disease on the functional status. In this respect, the Physician's Global Assessment provides a good representation of the overall disease status. However, it is not an accurate indicator of disease activity in vasculitis.⁶ The Vasculitis Activity Index, like the BVAS score, consists of a number of rating scales, but suffers from the disadvantage that it does not differentiate chronic damage from acute disease.⁷ Other indices include the Disease Extent Index (ELK)⁸ and the Groningen Vasculitis Score.⁹ The Groningen Vasculitis Score was designed for use only in Wegener's granulomatosis and has the disadvantage that the assessment requires a biopsy, thus limiting its use.⁹

An ideal index should provide information on disease activity, distinguish the difference between new symptoms and chronic damage, provide information on functional status, prognosis, and be simple to complete with minimal inter-observer variability. In an attempt to derive such a uniform index, the Vasculitis Integrated Assessment Log (VITAL) was devised.¹⁰ This incorporates an assessment method (BVAS), a damage index (Vasculitis Damage Index) and a functional assessment (Short-Form-36). VITAL was devised by the European Study Group for Therapeutic Trials in Systemic Vasculitis (ECSYSVAS-TRIAL), and if validated will provide a valuable tool for uniform data collection. Disease assessment scores can provide important information on disease activity but do not obviate the need for careful evaluation and should be used in conjunction with the biochemical and serological markers of disease currently available.

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Aberrant laboratory findings suggestive of active vasculitis

The laboratory tests should be used in conjunction with clinical acumen to diagnose active vasculitis, and should never be used in isolation. All of these tests, with perhaps the exception of the ANCA assay, lack specificity and can be raised in conditions other than systemic vasculitis

Haematology:

- ↓ haemoglobin
- ↑ leucocytes, platelets, eosinophils
- ↑ ESR, plasma viscosity

Biochemistry:

- ↑ urea, creatinine
- deranged liver function tests
- ↑ C-reactive protein, von Willebrand factor

Urine:

- proteinuria
- haematuria
- granular and cell casts

Immunology:

- ↑ IgG (polyclonal)
- rising ANCA titres or conversion from ANCA-negative to ANCA-positive

Box 1

Histopathology

Histopathology provides definitive evidence of organ involvement, as well as information on the severity of the vasculitic process and the extent of damage. A biopsy should only be performed if there is clinical evidence of disease in that organ. In practice, serial biopsies are not usually performed, unless there is inadequate response to treatment. The nasal mucosa provides a readily accessible site for biopsies in patients with Wegener's granulomatosis. Renal involvement in the form of a necrotising glomerulonephritis is associated with some forms of small vessel vasculitis such as Wegener's granulomatosis or microscopic polyangiitis. Obtaining renal histology in these cases provides information on disease status, and enables therapeutic decisions to be made on the type and duration of treatment.

Haematology and biochemistry (box 1)

Anaemia, of the normochromic normocytic type, is commonly present in the active phase of the disease. Occasionally, the anaemia can be of the iron deficiency type secondary to gastrointestinal tract or lung haemorrhage.¹¹ Other haematological abnormalities include neutrophil leucocytosis and thrombocytosis. However, steroid and immunosuppressive effects on leucocyte and platelet counts reduce the value of these tests in monitoring disease activity. An eosinophilia is a characteristic feature of Churg-Strauss syndrome but may also be found in polyarteritis nodosa.

Liver function tests may be deranged; hypoalbuminaemia, hyperglobulinaemia and a raised alkaline phosphatase can all be found in active disease.^{5 12} A deterioration in the serum urea and creatinine in a patient who has previously had stable renal function may indicate a relapse. Likewise, the emergence of haematuria, worsening proteinuria and particularly an active urinary sediment with red cells and casts, are suggestive of relapse. Changing and aberrant laboratory parameters together with the emergence of new clinical symptoms are strong indicators of active disease.

Acute phase proteins and von Willebrand factor (factor VIII-related antigen) (box 2; figure)

There are approximately 30 acute phase proteins, with the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) being the prototypes. The ESR is a laboratory measurement of the rate of sedimentation of erythrocytes, is affected by age and sex and is dependent on the packed cell volume and the degree of cell aggregation. Thus, the ESR is affected by conditions that affect the number and morphology of the red blood cells, such as anaemia. Aggregation in

Characteristic inflammatory markers of disease

- ESR: non-specific; long half life, and may not mirror disease activity; affected by age, sex, packed cell volume, protein molecules, fibrinogen levels
- plasma viscosity: non-specific; long half life, and may not mirror disease activity; affected by protein molecules, fibrinogen levels
- C-reactive protein: non-specific; short half-life of 6–10 h; correlates more closely with the events of inflammation
- von Willebrand factor: non-specific; synthesised by megakaryocytes and endothelial cells; levels reflect vascular injury
- ANCA: more specific for the vasculitides; long half-life (three weeks), thus ANCA titres fall will lag behind disease activity; rise in ANCA titres may predict a relapse
- serum markers of T-cell activation (IL-2 receptors): non-specific; assay not routinely available
- cytokines and soluble adhesion molecules (ICAM-1 and VCAM-1 adhesion molecules): non-specific; assay not routinely available

Box 2

turn is influenced by a number of large proteins, including fibrinogen, α_2 -macroglobulin and immunoglobulin, and so changes in the levels of these composite proteins will affect the ESR. Not surprisingly therefore, a raised ESR is not specific for active disease.⁶ Moreover, ESR relates poorly to the time course of inflammation as fibrinogen has a long half-life. Alternatively, plasma viscosity can be used to monitor disease activity, but like the ESR, its levels are affected by protein molecules and fibrinogen.

C-Reactive protein (CRP) is a non-glycosylated protein synthesised by the liver. It has a short half-life and rises rapidly within 6–10 hours of an inflammatory event. It is a more sensitive and specific marker of inflammation, correlating more closely with the events of inflammation.¹³ Several studies have reported a correlation between CRP concentrations and disease activity in Wegener's granulomatosis and microscopic polyarteritis; it has a useful albeit limited value in predicting increasing disease activity since some, but not all relapses may be associated with a rise in CRP.^{13–16} Nonetheless, like the ESR and plasma viscosity, its level can be affected by sepsis and differentiation between sepsis in an immunosuppressed patient and recrudescence of disease activity can be difficult. The von Willebrand factor is a large multimeric protein, synthesised by megakaryocytes¹⁷ and endothelial cells¹⁸ and levels reflect vascular injury. High plasma concentrations have been reported in a variety of diseases affecting blood vessels including vasculitis but raised levels can be found in inactive disease.^{19–20}

In summary, the ESR, plasma viscosity, CRP and von Willebrand factor are capable of reaching very high levels during active disease but none is specific for systemic vasculitis; their usefulness in monitoring disease activity has to be interpreted in this light. Despite such reservations, these inexpensive tests are easy to perform, and are available in most laboratories. Since CRP has a relatively short half-life, levels correlate more closely to disease activity than ESR or plasma viscosity, and can be used to monitor the response to treatment. Used together with clinical acumen, a combination of these assays will improve the specificity for disease monitoring.

Antineutrophilic cytoplasmic antibodies

Antibodies directed against neutrophil cytoplasmic antigens (ANCA), in particular proteinase-3 and myeloperoxidase, have been found to be strongly associated with Wegener's granulomatosis and other forms of idiopathic necrotising vasculitis and crescentic glomerulonephritis.^{21–24} Their value in the diagnosis of vasculitis is well established but their role in monitoring disease activity is perhaps more controversial.

Early reports revealed that ANCA levels were higher during active disease than during remission.^{23–26} A number of studies showed that ANCA titres either fell or disappeared with treatment, suggesting they are useful not only in the diagnosis but also in follow-up studies to assess disease activity and response to treatment.^{25–28} Moreover, a number of prospective studies have shown relapses to be preceded by a rise in ANCA titre and some investigators have suggested that clinical relapses can be pre-empted by early changes in therapy consequent on the rise in ANCA. Cohen Tervaert *et al* examined this hypothesis and randomly allocated asymptomatic patients with a significant rise in ANCA titre to either immunosuppressive treatment or no treatment.²⁹ During a 24-month follow-up

period, a significant rise in ANCA titre occurred in 20 patients. None of the treated patients had a relapse, but nine of 11 untreated patients had an exacerbation, ie, the predictive value of a rise in ANCA for subsequent relapses was 100%. However others have noted a dissociation between rises in antibody titres and clinical activity and have found that ANCA titre changes are not a sensitive marker of impending relapse.²⁸⁻³⁰ The dichotomy remains that in some patients ANCA titres have correlated with disease severity, while in others with severe forms of the disease ANCA titres have been low.²⁷⁻³¹ There are also patients who remain ANCA positive while in complete remission, or ANCA negative while still having active disease.³⁰⁻³² Moreover, a proportion of patients with vasculitis do not test positive for ANCA even at initial diagnosis,³³ and ANCA monitoring in these patients will have limited clinical relevance. On balance, there is a reasonable correlation between disease activity and ANCA titres and although a rise in ANCA titre is not entirely specific for a relapse, any observed titre rises should prompt careful re-evaluation of the patient for clinical evidence of active disease.

Given the controversial debate about the value of a rising ANCA titre in an asymptomatic patient, we advocate that caution should be exercised before initiating or escalating treatment based solely on ANCA titres, as the risk of over-treatment with immunosuppressive drugs is clearly present. Similarly, patients in whom ANCA persist appear to be at greater risk of relapse, unlike those who are persistently negative.³⁴ The presence of ANCA may therefore be a marker of those patients who need closest follow-up, and who may benefit from long-term immunosuppressive therapy.

ANCA titres may be useful in distinguishing relapses from other intercurrent illnesses particularly infections which are always a threat to patients on immunosuppressive therapy (figure). IgG has a half-life of about three weeks, thus care must be exercised in interpreting ANCA titres within two to three months of vasculitic relapse.

Serum markers of T-cell activation

Apart from humoral mechanisms, cell-mediated immunity may also be involved in the pathogenesis of vasculitis. IL-2 receptors are expressed and released by predominantly activated T-cells, and elevated levels of IL-2 receptors have been found in patients with Wegener's granulomatosis during major relapses.³⁵⁻³⁶ In one study, there was a close correlation between a rise in IL-2 receptor levels, ANCA titres, CRP and disease activity.³⁶ The use of IL-2 receptors in disease monitoring is restricted as levels are also raised in infections.³⁷⁻³⁸

Figure Serial measurements of ESR, CRP, and cANCA titres shown in relation to clinical course in a patient with Wegener's granulomatosis. With active disease, both at presentation and at relapse, all three markers were raised. During an episode of infection, however, only ESR and CRP were raised, while ANCA remained low. ANCA can be a useful marker for distinguishing disease relapse from infections. CRP has a short half-life and levels fell rapidly with treatment. It is therefore a useful marker for monitoring disease and early response to treatment. In contrast, both ESR and ANCA have long half-lives and levels take much longer to fall; care should be taken in interpreting levels soon after active disease or infection. P = prednisolone; C = cyclophosphamide; PEX = plasma exchange

Investigations in suspected vasculitis relapse

- take a comprehensive history, looking for symptoms of a systemic illness
- conduct a thorough examination looking for signs of an active vasculitic illness, such as rash, uveitis, arthritis and other organ involvement
- look for laboratory evidence of inflammation as outlined in boxes 1 and 2
- radiology may provide confirmatory evidence of lower respiratory tract involvement
- examine the urine for casts and red blood cells; perform urinalysis looking for proteinuria and/or haematuria
- serial use of a validated disease activity index can provide an assessment of activity, extent of damage and response to treatment
- biopsy of an affected organ will provide definitive evidence of involvement, and should be considered in cases of disease ambiguity

Box 3

Cytokines and soluble adhesion molecules

Roche *et al* found increased IL-6 levels in patients with polymyalgia rheumatica and giant cell arteritis.³⁹ However, although there was a close correlation between the ESR, platelet counts and IL-6 levels in patients monitored longitudinally, there was no correlation for the entire study population. This would suggest that apart from IL-6, other factors must contribute towards the inflammatory response. Indeed, elevated levels of tumour necrosis factor, IL-2, IL-6, IL-8, interferon- α , soluble ICAM-1 and VCAM-1 adhesion molecule have been described in acute vasculitis.⁴⁰⁻⁴⁶ In general, there has been inconsistent association with disease activity and cytokine assays are not yet routinely available in most laboratories. Until these problems can be overcome, it is likely that they will remain research tools only.

Conclusion

The best objective guide to disease activity in vasculitis remains clinical assessment, preferably in conjunction with a validated scoring system. Although a rise in ANCA titre is not entirely specific for a relapse, any observed titre rises should prompt re-evaluation of the patient for clinical evidence of active disease. Measurement of non-specific indices of inflammation such as CRP is useful, particularly in patients with ANCA-negative vasculitis. In cases of uncertainty, histopathology provides definitive information on disease status. We suggest that clinical signs of disease, supplemented by a validated scoring system and laboratory measurements of disease, including ANCA, and, as appropriate, by tissue biopsy should be used to complement each other in monitoring disease activity.

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