EXAMINATION OF DISEASE SEVERITY IN SYSTEMIC VASCULITIS FROM THE NOVEL PERSPECTIVE OF DAMAGE USING THE VASCULITIS DAMAGE INDEX (VDI)

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SUMMARY
Assessment of disease severity in systemic vasculitis encompasses mortality, which is now uncommon, and morbidity, which is increasing in significance. Morbidity includes permanent scars or damage, an evolving concept offering a novel perspective which may be particularly valuable in chronic disease. We have developed a method for assessing damage in systemic vasculitis, but the relationship between damage and disease severity was unknown. Therefore, we examined whether the number of items of damage or the pattern of damage varied with the severity of systemic vasculitis. We established the characteristics of severe disease by examining fatal vasculitis as an example of the most severe disease possible. We then showed that more damage occurred in fatal vasculitis, more systems were damaged, and critical damage akin to organ failure was more common in fatal than non-fatal vasculitis. These observations were reproduced in specific diagnostic groups, namely classical Wegener’s granulomatosis and systemic rheumatoid vasculitis. Thus, severe disease was characterized by many items of damage, multisystem damage and critical damage. This pattern of damage was also seen in a subgroup of patients with non-fatal vasculitis, who also have severe disease.

KEY WORDS: Damage, Disease severity, Outcome, Systemic vasculitis.

The classical image of systemic vasculitis as an acute, progressive, fatal disease [1, 2] has been substantially modified by current treatment. The use of cyclophosphamide treatment has dramatically improved acute survival [3, 4], but this has not provided the hope for cure. The systemic vasculitides have become chronic relapsing diseases with >50% of patients suffering a relapse within 5 yr of remission [5]. Half the patient-years of follow-up are accounted for by active or only partially suppressed disease due to disease relapse and a poor initial response in some patients. The current cost of inducing clinical remission is serious morbidity attributable to disease or drug toxicity in over half of the patients treated [6]. Thus, death from systemic vasculitis is uncommon and is often a late event, but morbidity is common and highly variable. Both mortality and morbidity contribute to disease severity, and can be used in the assessment of outcome. Measurement of disease severity may facilitate patient stratification in clinical trials and the evaluation of laboratory markers of prognosis.

A comprehensive assessment of disease severity should incorporate measurements of disease activity, damage and functional status [7]. Each element reflects different concepts which together contribute to outcome and quality of survival. We have previously described a measure of disease activity, the Birmingham Vasculitis Activity Score [8], which was based on an assessment of the intention to treat active, potentially reversible disease. Current treatment regimens incorporating cytotoxic drugs have a narrow therapeutic range. This underlines the need to distinguish potentially reversible disease activity from damage or scarring which is unlikely to respond to immunosuppression. Damage is an evolving concept which may be a more appropriate index of disease severity and outcome in chronic diseases [9]. We therefore developed the Vasculitis Damage Index (VDI) as a clinical tool for the standardized measurement of damage [10].

Initial validation indicates that the VDI is a sensitive, reproducible, comprehensive and credible clinical instrument for recording the accumulation of damage [10]. The VDI compares favourably with other damage indices developed for systemic lupus erythematosus or reported in a comparison of patients with polyarteritis nodosa and Churg–Strauss syndrome [11, 12]. Standardized assessment showed that the VDI recorded more items of damage, both at a single assessment and serially, which suggested it should be more sensitive to change in systemic vasculitis [10], but it remained to be established whether there was any correlation between damage and disease severity. In the present study, we examine whether the pattern or extent of damage varies with the severity of systemic vasculitis. We establish the characteristics of severe disease by examining 20 cases of fatal vasculitis, representing the most severe disease.

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possible. We measure damage in fatal and non-fatal systemic vasculitis and compare these groups. We show that fatal systemic vasculitis has a distinct pattern of damage. We then use this pattern of damage to identify a subgroup with non-fatal vasculitis, who by implication also have severe disease.

**PATIENTS AND METHODS**

**Subjects**

This is an observational study of 20 cases of fatal systemic vasculitis and 100 cases of non-fatal systemic vasculitis from the University of Birmingham Vasculitis Clinics. The patients’ demographic details and diagnoses are shown in Table I. The diagnosis of systemic vasculitis, including systemic rheumatoid vasculitis and Behçet’s syndrome, was made according to accepted criteria [8, 13, 14]. Patients with Churg–Strauss syndrome, giant cell arteritis, Henoch–Schönlein purpura, polyarteritis nodosa, Takayasu’s arteritis and Wegener’s granulomatosis were classified according to the ACR 1990 criteria [15–20]. Patients with microscopic polyangiitis were defined using the Chapel Hill consensus definitions [21]. Patients with Wegener’s granulomatosis were subdivided into classical (renal) and localized (non-renal) Wegener’s granulomatosis [22].

**Measurements**

Data were collected on all patients retrospectively by chart review, including patients with non-fatal vasculitis who were seen as part of prospective follow-up studies between July 1993 and December 1995. Duration of disease was from the first symptoms attributable to vasculitis to the last observation prior to death in fatal vasculitis and the last clinic visit for non-fatal vasculitis. The VDI is a tabulated list of 64 items of damage, grouped into 11 organ-based systems, namely musculoskeletal, skin, ear nose and throat (ENT), pulmonary, cardiovascular, peripheral vascular, renal, gastrointestinal, ophthalmic, neuropsychiatric, and other damage/drug toxicity. Ease of use is enhanced by incorporating guidelines for applying the VDI, and a glossary to assist recording the presence or absence of damage [10]. Assessments can be rapidly completed by checking the few items of damage sustained in the VDI proforma [10] (listed in Appendix 1). The VDI is cumulative since items of damage scored at earlier time points are carried forward to all subsequent assessments. Damage is expressed using two general scores: the total VDI score, which is the sum of individual items of damage scored in each patient since the onset of disease; and the systems score, which is the number of individual systems in each patient which have scored at least one item of damage [10].

The design of the VDI enables the characteristics of damage to be analysed in a number of different ways. Damage can be analysed within each of the 11 systems across a cohort of patients. Consensus amongst a nominal group of experts in vasculitis was established to select items of damage regarded as clinically significant. Thus, three analytical scores were derived for critical damage (the sum of items of damage consistent with significant organ failure), treatment-related damage (the sum of items of damage attributable in major part to drug toxicity) and major vascular damage (the sum of items of damage to major blood vessels attributable to disease and or complications such as atheroma) (Appendix 1 and 2). In these analyses, each item of damage is scored as present (1) or absent (0), yielding a maximum score of 16 for critical damage, 9 for treatment damage and 10 for major vascular damage.

**Statistical analysis**

Statistical analysis was performed using Minitab for Windows, Release 10.2 (Minitab Inc., State College, PA, USA). Non-parametric tests were used throughout, expressed as median values and interquartile ranges unless stated otherwise. The Wilcoxon signed rank test was used for comparison of paired data, and the Mann-Whitney test for comparison between two groups. All tests were two-tailed unless otherwise stated. The χ² test was used to compare the number of patients in the two groups with critical

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>Age</th>
<th>Duration of disease</th>
<th>Diagnosis</th>
<th>No.</th>
<th>Age</th>
<th>Duration of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic rheumatoid vasculitis</td>
<td>8</td>
<td>70 (55–76) yr</td>
<td>7.3 (2.0–8.1) yr</td>
<td>Polyarteritis nodosa</td>
<td>12</td>
<td>61 (47–67) yr</td>
<td>5.8 (4.5–10.4) yr</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>12</td>
<td>61 (47–67) yr</td>
<td>5.8 (4.5–10.4) yr</td>
<td>Classical Wegener’s granulomatosis</td>
<td>22</td>
<td>55 (38–67) yr</td>
<td>5.3 (2.6–9.2) yr</td>
</tr>
<tr>
<td>Classical Wegener’s granulomatosis</td>
<td>22</td>
<td>55 (38–67) yr</td>
<td>5.3 (2.6–9.2) yr</td>
<td>Takayasu’s arteritis</td>
<td>7</td>
<td>53 (38–67) yr</td>
<td>8.7 (8.2–11.6) yr</td>
</tr>
<tr>
<td>Non-renal Wegener’s granulomatosis</td>
<td>27</td>
<td>49 (40–64) yr</td>
<td>6.1 (3.2–10.6) yr</td>
<td>Behçet’s disease</td>
<td>7</td>
<td>42 (41–49) yr</td>
<td>17.8 (7.6–24.3) yr</td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td>7</td>
<td>53 (38–67) yr</td>
<td>8.7 (8.2–11.6) yr</td>
<td>Churg–Strauss syndrome</td>
<td>7</td>
<td>52 (44–61) yr</td>
<td>9.1 (6.8–11.2) yr</td>
</tr>
<tr>
<td>Churg–Strauss syndrome</td>
<td>7</td>
<td>52 (44–61) yr</td>
<td>9.1 (6.8–11.2) yr</td>
<td>Microscopic polyangiitis</td>
<td>10</td>
<td>67 (43–74) yr</td>
<td>3.9 (2.6–5.1) yr</td>
</tr>
<tr>
<td>All</td>
<td>100</td>
<td>54 (42–66) yr</td>
<td>6.1 (3.4–10.1) yr</td>
<td>All</td>
<td>100</td>
<td>54 (42–66) yr</td>
<td>6.1 (3.4–10.1) yr</td>
</tr>
</tbody>
</table>

Patients are grouped by diagnosis. Age and duration of disease are shown as median and interquartile ranges. Values for patients with non-fatal disease and severe fatal disease were compared: **=not significant; *P = 0.04; †P < 0.001.**

$P = 0.04; \quad < 0.001.$
damage, major vascular damage and treatment-related damage. The potential to discriminate between severe fatal disease and non-fatal disease using damage was tested by generating receiver operating characteristic curves for the VDI score, systems score and critical damage score. The odds ratio [with 95% confidence limits (CI)] was calculated [23] for severe fatal disease by applying thresholds of a total VDI score \( \geq 5 \), a systems score \( \geq 3 \) and a critical damage score \( \geq 1 \) to all patients at final observation.

**RESULTS**

**Total damage**

We first examined the number of items of damage sustained during long-term follow-up. At presentation, there was no significant difference between patients with non-fatal disease and severe fatal disease. At final observation, patients with severe fatal disease had higher total VDI scores than patients with non-fatal disease: median score 7 vs 4 (\( P = 0.0001 \)) (Fig. 1A). Excess damage in severe fatal disease occurred within a shorter time frame: median 2.6 yr in severe fatal disease vs 6.1 yr in non-fatal disease (\( P < 0.001 \)) (Table I).

**Damage within organ-based systems**

We next examined the spread of organ systems involved in the total damage. There was no difference between severe fatal disease and patients with non-fatal disease at presentation. At final observation, damage in many systems was seen in severe fatal disease: median systems score 5 vs 3 (\( P < 0.0001 \)) (Fig. 1B).

**Key items of damage**

The clinical significance of damage varies between different items within the VDI. Analytical/selective scores for critical damage, treatment-related damage and major vascular damage highlighted differences between severe fatal disease and patients with non-
fatal disease (Fig. 3). Patients with severe fatal disease were more likely to have critical damage ($\chi^2 = 27.2, \text{d.f.} = 2, P < 0.001$) and major vascular damage ($\chi^2 = 6.7, \text{d.f.} = 1, P = 0.01$). Treatment-related damage did not differ significantly between severe fatal disease and non-fatal disease ($\chi^2 = 3.0, \text{d.f.} = 2, P = 0.2$).

Treatment-related damage did not differ significantly between severe fatal disease and non-fatal disease ($\chi^2 = 3.0, \text{d.f.} = 2, P = 0.2$). Treatment-related damage was analysed for all 120 patients according to the patients’ age, dividing patients into an older group $\geq 60$ yr old at presentation ($n = 39$) and a younger group aged $< 60$ yr at presentation ($n = 81$). This analysis revealed an excess of treatment-related damage in older patients, affecting 46% of older patients vs 21% of younger patients ($P = 0.004$).

**Damage in specific diagnostic groups**

We then determined whether these analyses were applicable in specific diagnostic groups. We examined, from the perspective of damage, examples of primary necrotizing systemic vasculitis and secondary systemic vasculitis, namely classical Wegener’s granulomatosis and systemic rheumatoid vasculitis.

**Table II**

<table>
<thead>
<tr>
<th>Thresholds</th>
<th>Odds ratios for severe fatal disease (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VDI score $\geq 5$</td>
<td>6.4 (2.1–19.0)</td>
</tr>
<tr>
<td>Systems score $\geq 3$</td>
<td>13.2 (1.7–102.5)</td>
</tr>
<tr>
<td>Critical damage score $\geq 1$</td>
<td>17.5 (2.3–136.1)</td>
</tr>
</tbody>
</table>

Thresholds for the total VDI score, systems score and critical damage score which might discriminate between severe fatal disease and non-fatal disease were determined by reviewing the distribution of data (Figs 1 and 3). Odds ratios with 95% confidence intervals for severe fatal disease vs non-fatal disease were calculated.

(Table I). In classical Wegener’s granulomatosis, the total VDI score at final observation was higher in severe fatal disease ($n = 11$) than in patients with non-fatal disease ($n = 22$): median total VDI score 7 vs 4 ($P = 0.02$). Damage in many systems was again a characteristic of severe fatal disease: median systems score 6 vs 3 ($P = 0.02$). Critical damage scores were higher in severe fatal disease than in patients with non-fatal disease, 1 (0–4) vs 0.5 (0–1) ($P = 0.001$). Similar trends were evident in patients with systemic rheumatoid vasculitis. The total VDI score at final observation was higher in severe fatal disease ($n = 7$) than in patients with non-fatal disease ($n = 8$): median total VDI score 5 vs 3 ($P = 0.03$). Damage in many systems was seen in severe fatal disease: median systems score 4 vs 3 ($P = 0.049$).

**Damage as a discriminator between severe fatal disease and non-fatal disease**

We examined whether damage was a powerful discriminator between severe fatal disease and non-fatal disease at final observation by applying three differ-
ent damage thresholds. Odds ratios for severe fatal disease vs non-fatal disease were calculated using thresholds of a total VDI score $\geq 5$, a systems score $\geq 3$ and a critical damage score $\geq 1$ (Table II). Each threshold proved a good discriminator for severe fatal disease with odds ratios from 6.4 to 17.5. Receiver operating characteristic curves (Fig. 4) show that these thresholds have a high sensitivity, but ‘misclassify’ some patients with non-fatal disease. Indeed, a subgroup of patients with non-fatal vasculitis share the same pattern of damage as patients with fatal systemic vasculitis.

**DISCUSSION**

Assessment of disease severity encompasses both mortality and morbidity. In systemic vasculitis, morbidity despite cytotoxic therapy is common. Recent studies identified serious morbidity attributable to disease or drug toxicity in over half the patients treated [6]. Morbidity includes permanent scars or damage, an evolving concept offering a novel perspective which may be particularly valuable in chronic disease. We developed a method for assessing damage in systemic vasculitis [10], but the importance of damage was unclear. Therefore, we examined whether the number of items of damage or the pattern of damage varied with the severity of systemic vasculitis. We established the characteristics of severe disease by examining cases of fatal vasculitis, representing the most severe disease possible. We showed that more items of damage were sustained, more systems were damaged and critical damage akin to organ failure was more common in fatal than non-fatal vasculitis. These observations were reproduced in specific diagnostic groups, namely classical Wegener’s granulomatosis and systemic rheumatoid vasculitis. Thus, the characteristics of severe disease were many items of damage, multisystem damage and critical damage. This pattern of damage was also seen in a subgroup of patients with non-fatal vasculitis, who by implication also have severe disease.

Severe fatal disease was characterized by more items of damage accumulated within a shorter time frame. Damage was spread across many systems in severe disease. Patients with severe disease were more likely to have multiple items of damage in most of the organ-based systems. Selective analyses highlighted particular aspects of damage associated with severe fatal disease such as items of critical damage akin to multi-organ failure [10, 24]. The relationship between damage and severe disease within the whole patient cohort was confirmed by similar findings within subgroups representing common examples of primary systemic necrotizing vasculitis and secondary systemic vasculitis. Excess damage in severe disease was a feature of all the organ systems with the sole exception of ENT damage. In contrast, multiple items of ENT damage were a feature of less severe disease. ENT damage can be disfiguring and might be expected to affect the quality of survival. Subglottal stenosis can severely compromise respiratory function unless treated aggressively [25]. Thus, the clinical significance of damage varies within the VDI.

Patients with severe fatal disease were more likely to sustain major vascular damage involving limb, cerebral and coronary vessels. Such damage might reflect disease, hypertension and/or accelerated atheroma as a complication of treatment. Attribution of damage is controversial [10], but these findings emphasize the narrow therapeutic margins of current therapies. Treatment-related damage appeared unrelated to disease severity, but was seen particularly in older patients. This supports recent data on the risks of treating elderly patients, and complications of long-term cytotoxic therapy in systemic vasculitis [6, 26, 27]. Prospective studies are required to examine whether treatment-related damage reflects the need to control more aggressive disease. The relationship between disease activity and damage requires further detailed examination.

Patients with severe fatal disease accumulated more damage despite a shorter duration of illness, indicating a more aggressive disease. Serial assessment showed that damage occurred early, especially in severe disease; early damage was disease-related damage and was an index of disease severity [28]. Together, these data suggest that measurement of damage may contribute to assessment of outcome. Measurement of damage might also contribute to patient stratification in clinical trials and evaluation of laboratory markers of prognosis. There are precedents for this approach. Identification of prognostic markers early in the course of a chronic disease has important implications for treatment. Evidence is accumulating that early joint damage is a marker of poor prognosis in rheumatoid arthritis [9]. Renal impairment is a marker of poor prognosis in acute systemic vasculitis [29] and in our series was a feature of severe fatal disease. This observation suggests that it may be possible to re-examine the evidence that renal disease is a poor prognostic marker by comparing patients with and without renal damage in a larger cohort or in a specific disease.

These data suggest the VDI is a powerful clinical tool for measuring relevant damage. The tabulated design of the VDI makes it easy to use within the clinical routine, and a computerized version is available as part of the assessment of disease activity, damage and functional status [30]. The design of the VDI incorporates general scores of total damage and analytical/selective scores. Individual items or a number of items of damage can be selected to investigate the clinical significance of damage. This study delineated the extent of damage that accumulated in systemic vasculitis and demonstrated a quantifiable relationship between damage and disease severity. We showed that damage at last observation may be an index of disease severity, and this was supported by serial studies [28]. Prospective studies
are required to investigate whether there are consistent thresholds of damage for optimal discrimination of disease severity.

Previous work has largely focused on mortality and disease activity in vasculitis. The current work establishes that damage is an equally important parameter to study in these diseases. Damage provides a different perspective on chronic diseases, which is a relevant and quantifiable surrogate for mortality. This is particularly important now that early mortality is largely controlled by therapy. Prevention of damage must be the aim of future therapy, while recognition of the contribution of damage to morbidity should influence current patient management. The VDI should provide a powerful clinical tool to investigate patterns of disease as part of the global assessment of patients with systemic vasculitis [7]. This new clinical tool has practical and conceptual value, indicating that damage may offer a novel perspective on other chronic diseases.

ACKNOWLEDGEMENTS

We are grateful for the support of Dr Adu, Dr Savage and clinical colleagues who referred their patients for assessment. We thank members of the Birmingham Vasculitis Group, the European Concerted Action Group for the Study of Therapeutic Trials in Systemic Vasculitis, Dr Simon Bowman, Dr Caroline Gordon and Professor Jon Ayres for their help and advice. This work was supported in part by the Arthritis and Rheumatism Council, grant number B80.

REFERENCES

APPENDIX 1: ITEMS OF DAMAGE IN THE VASCULITIS DAMAGE INDEX

1. MUSCULOSKELETAL DAMAGE
   - Significant muscle atrophy or weakness
   - Deforming or erosive arthritis
   - Osteoporosis with fractures or vertebral collapse
   - Avascular necrosis
   - Osteomyelitis

2. SKIN DAMAGE
   - Alopecia
   - Skin ulceration
   - Oral ulceration

3. ENT DAMAGE
   - Hearing loss
   - Nasal blockage/chronic discharge/crusting
   - Nasal bridge collapse/septal perforation
   - Chronic sinusitis/radiological evidence of bone destruction
   - Subglottal stenosis without surgery
   - Subglottal stenosis undergoing surgery

4. PULMONARY DAMAGE
   - Pulmonary hypertension
   - Pulmonary fibrosis/cavity
   - Pleural fibrosis
   - Pulmonary infarction: Chronic asthma:
     - Significant chronic breathlessness
     - Impaired pulmonary function tests
     - Significant abnormality of pulmonary function

5. CARDIOVASCULAR DAMAGE
   - Angina/coronary artery bypass
   - Myocardial infarction
   - Second myocardial infarction
   - Cardiomyopathy

APPENDIX 2: GENERAL AND ANALYTICAL SCORES WITHIN THE VASCULITIS DAMAGE INDEX

<table>
<thead>
<tr>
<th>Score</th>
<th>Sum</th>
<th>Maximum range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VDI score</td>
<td>All items of damage since onset of disease</td>
<td>0–64</td>
</tr>
<tr>
<td>Systems score</td>
<td>Number of systems with ≥1 item of damage</td>
<td>0–11</td>
</tr>
<tr>
<td>Critical damage</td>
<td>Items consistent with significant organ failure</td>
<td>0–16</td>
</tr>
<tr>
<td>Treatment-related damage</td>
<td>Items primarily attributable to drug toxicity</td>
<td>0–9</td>
</tr>
<tr>
<td>Major vascular damage</td>
<td>Items of damage to major blood vessels attributable to disease and/or complications such as atheroma</td>
<td>0–10</td>
</tr>
</tbody>
</table>

Valvular disease
Pericarditis
Hypertension

6. RENAL DAMAGE
   - Estimated or measured GFR < 50%
   - Proteinuria of > 0.5 g/24 h
   - End-stage renal failure

7. GASTROINTESTINAL DAMAGE
   - Gut infarction
   - Mesenteric insufficiency/pancreatitis
   - Chronic peritonitis
   - Oesophageal stricture OR upper gastrointestinal tract surgery

8. PERIPHERAL VASCULAR DAMAGE
   - Absent peripheral pulse in one limb
   - Second episode of absent peripheral pulse in one limb
   - Absent peripheral pulses in ≥2 limbs
   - Major vessel stenosis
   - Claudication
   - Complicated venous thrombosis
   - Minor tissue loss
   - Major tissue loss
   - Second episode of major tissue loss

9. OCULAR DAMAGE
   - Cataract
   - Retinal change
   - Optic atrophy
   - Visual impairment/diplopia
   - Blindness in one eye
   - Blindness in second eye
   - Orbital wall destruction
   - Significant bone destruction as documented on X-ray/CT/MRI

10. NEUROPSYCHIATRIC DAMAGE
    - Cognitive impairment
    - Major psychosis
    - Seizures
    - Cerebrovascular accident
    - Second cerebrovascular accident
    - Cranial nerve lesion
    - Peripheral neuropathy
    - Transverse myelitis

11. OTHER DAMAGE/DRUG TOXICITY
    - Premature gonadal failure
    - Marrow failure
    - Diabetes mellitus
    - Chronic chemical cystitis
    - Malignancy