Rheumatoid vasculitis: becoming extinct?

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**Background.** Systemic rheumatoid vasculitis (SRV) is a relatively rare complication of RA. The incidence of SRV appeared to increase during the 1970s and 1980s from 6.0 to 12.5/million. During the 1990s there have been major changes in the treatment of RA, with more aggressive control of inflammation. Our aim was to study the epidemiology of SRV in a stable, well-defined population over a 15-yr period.

**Methods.** Since 1988 we have maintained a prospective register of all patients with systemic vasculitis attending the Norfolk and Norwich University Hospital. Patients presenting with new-onset SRV, as defined by the criteria of Scott and Bacon, and registered with general practitioners in the former Norwich Health Authority area between 1988 and 2002 were identified. The population in 2002 was estimated to be 445 000 (215 000 males).

**Results.** Fifty-one patients (24 male) with SRV were identified, with median age 61 yr and disease duration 16.8 yr. The overall annual incidence was 7.9/million (95% CI 5.9–10.4) (males, 7.7/million; females, 8.1/million). During the first quinquennium (1988–92) the incidence was 11.6/million (95% CI 7.4–17.0) and during the third (1998–2002) it was 3.6/million (95% CI 1.6–7.1). A rolling 3-yr average showed that the peak incidence was in 1992–94, at 15.2/million (95% CI 9.1–23.8), and the nadir was in 1998–2000, at 3.0/million (95% CI 0.8–7.8). A similar pattern was seen for males and females. There was no difference in age or disease duration at onset of SRV between the three quinquennia.

**Conclusions.** The incidence of SRV has declined dramatically since the 1980s. This could be due to better control of inflammatory disease or changes in smoking habits.

Vasculitis occurring in RA (systemic rheumatoid vasculitis, SRV) was first described over 100 yr ago, in a patient with involvement of the vasa nervorum, and the clinical association was clearly established during the 1940s and 50s [1]. It is now recognized as a relatively rare complication that usually occurs in patients with long-standing seropositive erosive nodular RA. There is considerable associated morbidity and mortality [2].

The incidence of SRV appeared to increase during the 1970s and 1980s. The first estimate of the annual incidence of SRV was from Bristol in the 1970s; this study reported an incidence of 6.0/million [3]. In Norfolk during 1988–94 we reported an annual incidence of 12.5/million [4]. It was considered that a possible explanation for the increasing incidence of SRV was the extensive use of corticosteroids to control disease activity, often in doses that would by modern standards be considered excessive. However, it is not possible to exclude better case recognition. A study from Spain reported an incidence of biopsy-proven SRV of 6.4/million (males, 6.5/million; women, 6.2/million) during 1988–97 [5].

During the 1990s there have been major changes in the treatment of RA, with increased emphasis on early diagnosis and the introduction of DMARDs, together with aggressive control of inflammation, as assessed by plasma CRP [6]. There have been developments in drug therapy, with more widespread use of methotrexate (often as initial therapy), combination therapy and, most recently, biological agents to block TNF-\(\alpha\). If SRV is a consequence of uncontrolled inflammation, these changes in therapeutic approach should result in a decrease in the incidence of SRV.

We have since 1988 maintained a prospective register of patients with systemic vasculitis who attend the Norfolk and Norwich University Hospital (NNUH), which is the single central referral centre for a stable and ethnically homogeneous population of approximately 500 000. The study area covers a geographically isolated coastal region in Eastern England, allowing the population to be well defined and therefore suitable for epidemiological studies over a prolonged period [7]. The aim of the present study was to establish the incidence of SRV over a 15-yr period with particular reference to temporal changes.

**Patients and methods**

All patients attending the NNUH as out-patients, day admissions and hospitalized with a new clinical diagnosis of systemic vasculitis between 1 January 1988 and 31 December 2002 were recorded prospectively. Patients from the denominator population were identified. A retrospective review of the complete case notes was performed to confirm the diagnosis of SRV. The computerized records of the histopathology department were searched for patients with a histological diagnosis of vasculitis (renal and skin) and the case records were reviewed. Patients with a diagnosis of SRV were treated with intravenous pulse cyclophosphamide and/or pulse intravenous methylprednisolone, and therefore the records of the rheumatology day unit (where patients receiving intravenous cyclophosphamide were treated) were also reviewed. The hospital discharge diagnostic index was also searched for...
patients with a discharge diagnosis of systemic vasculitis using the International Classification of Diseases (9th and 10th revisions) codes.

Patients with a documented onset of SRV prior to 1988 were excluded, as were patients with other types of systemic vasculitis, such as Wegener’s granulomatosis, polyarteritis nodosa, microscopically polyangiitis, Churg–Strauss syndrome, Henoch–Schönlein purpura, hypersensitivity vasculitis, and vasculitis secondary to connective tissue disease.

SRV was defined using the Scott and Bacon criterion [8], i.e. the presence of one or more of the following in a patient with RA: (i) mononeuritis multiplex or peripheral neuropathy; (ii) peripheral gangrene; (iii) biopsy evidence of acute necrotizing arteritis plus systemic illness (e.g. fever, weight loss); (iv) deep cutaneous ulcers or extra-articular disease (e.g. pleurisy, pericarditis, scleritis) if associated with typical digital infarcts or biopsy evidence of vasculitis. Other causes of such lesions, such as atheroerosclerosis and diabetes mellitus, were excluded. Nailfold lesions were considered to be isolated if they occurred in the absence of any of the above features of SRV. All patients met the ARA criteria for RA [9]. A physician not directly involved in patient care (RAW) confirmed the diagnosis of vasculitis and classified the patients.

The denominator population was the same as that used in previous studies: patients registered with general practitioners in the former Norwich Health Authority [7]. The denominator adult population increased slightly during this period: in 1992 it was 413,500 (200,000 males) and in 1997 it was 429,000 (207,000 males). Changes in the structure of the National Health Service in England, with the abolition of the Norwich Health Authority, made it difficult to obtain accurate population data for 2002. We have therefore estimated the 2002 population assuming a linear rate of growth of 3.75%, using population growth estimates for the local population from the 2001 census [10]. The estimated 2002 population was 445,000 (215,000 males). The population was approximately 95% Caucasian of UK descent, which is lower than the average for England [10]. Around 9% of the population was aged >75 yr, which is higher than the average percentage for England [10]. The gender balance was similar to the UK as a whole.

Age- and gender-specific incidence rate were calculated using the number of incident cases as the numerator and the population as the denominator. Incidence rates were calculated during the three quinquennia (1988–92, 1993–97, 1998–2002). A rolling three-centred moving average was calculated to assess whether there were any peaks or troughs in incidence. The population living in each year was estimated by linear interpolation from the known populations (1992 and 1997), and by extrapolation as described above. Confidence intervals (95%) were calculated using the Poisson distribution.

The Norwich Local Research Ethics Committee approved the study.

Results

A total of 74 patients with a new diagnosis of SRV were identified during the period from 1 January 1988 to 31 December 2002. Of these patients, 51 (24 male) with SRV were from the denominator population and were included in the study. The remaining patients were not resident in the denominator population at the time of diagnosis or had an original diagnosis before 1988. All patients included in the study were identified from the prospective register and there were no additional cases from the alternative sources, such as histopathology or day unit records.

The median age at diagnosis of SRV for the whole cohort was 60.8 yr (range 23–81 yr) and the duration of RA before the onset of vasculitis was 16.0 yr (range 1–43). There was no difference between the three quinquennia in age at the onset of SRV (62.3, 59.4 and 59.0 yr respectively) and duration of RA prior to onset of SRV (15.3, 16.6 and 16.5 yr). Rheumatoid factor was present in 89% of patients, 80% had documented nodules, 40% were using corticosteroids at diagnosis and 90% had used corticosteroids at some stage in their illness. Methotrexate had been used at some time by 85% of patients. The major clinical features were cutaneous (infaracts, 70%; ulcers, 45%), peripheral neuropathy (34%), mononeuritis multiplex (12%) and pulmonary (28%).

The overall annual incidence of SRV during 1988–2002 was 7.9/million (95% CI 5.9–10.4). There was no significant difference in incidence between men [7.7/million (4.9–11.5)] and women [8.1/million (5.3–11.8)]. The annual incidence in the first quinquennium was 11.6/million (95% CI 7.4–17.0) and in the third quinquennium it was 3.6/million (95% CI 1.6–7.1) (Table 1). This decrease occurred in both males and females. A rolling 3-yr average showed that the incidence of SRV increased during the early 1990s, with a peak in 1992–94 of 15.2/million (95% CI 9.1–23.8), but declined quite quickly after 1995, with a nadir incidence of 3.0/million (95% CI 0.8–7.8) in 1998–2000 (Fig. 1). The peak incidence in women occurred in 1992–94, with an incidence of 18.6/million (95% CI 9.6–32.5) and a nadir incidence in 1997–99 of 0.5/million (95% CI 0.0–8.4). For men the peak was in 1991–93, with a zenith incidence of 13.3 (95% CI 5.7–26.3) and a nadir in 2000–02 of 3.1/million (95% CI 0.4–11.2).

Discussion

This study extends our previous report on the incidence of SRV in a stable population [4] and is the first to provide data on a stable cohort of patients collected prospectively over a 15-yr period. The results show that the incidence of SRV has declined quite markedly since the mid-1990s. We feel that the capture of patients was complete, as identification of patients from sources other than the registry did not reveal any additional patients. Patterns of care for patients with RA in our population have not changed over the last 15 yr, and are centred on the Norfolk and Norwich University Hospital. We are confident that there has not been leakage of patients to other hospitals. In the UK most patients with RA requiring DMARDs (especially methotrexate) are referred to secondary care. Changes in pattern of medical care have increased the tendency for primary care physicians to refer patients during the course of the study, so the likelihood of patients with severe disease (e.g. vasculitis or neuropathy) not being referred to secondary care during the duration of the study has decreased. As with any study of this nature, our estimates of incidence represent minima, but we feel that factors which would influence with complete identification of patients with SRV have not altered significantly in an adverse direction during the past 15 yr. The incidence of RA in the Norfolk Arthritis Register (NOAR) study (which used the same population as the present study) in 1990 was 36/100,000 for women and 14/100,000 for men [11]. It is at present too early to assess the incidence rate of SRV in the NOAR cohort.

Our results are consistent with a recent study of hospital admissions in California (USA), which showed that the rates of

<table>
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<th>Period</th>
<th>Incidence (total)</th>
<th>Incidence (males)</th>
<th>Incidence (females)</th>
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<tr>
<td>1988–92</td>
<td>24</td>
<td>12</td>
<td>12</td>
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<tr>
<td>1993–97</td>
<td>19</td>
<td>8</td>
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<td>1998–02</td>
<td>8</td>
<td>3</td>
<td>4</td>
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<tr>
<td>1998–02</td>
<td>51</td>
<td>24</td>
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Data are incidence per million population (95% CI).
hospital admissions for vasculitis in the context of RA was one third lower in 1998–2001 compared with 1983–87 [12]. Other manifestations of severe RA, such as splenectomy for Felty’s syndrome and surgery for cervical spine instability, were also reduced. This is in contrast to a recent retrospective review of 609 cases from Rochester (USA) diagnosed during 1955–94 which suggested that the incidence of extra-articular disease, including SRV, had not changed significantly over the decades [13].

Data from our registry suggest that the incidences of other types of vasculitis are stable if not increasing. During 1988–97, the incidence of primary systemic vasculitis (PSV) (Wegener’s granulomatosis, microscopic polyangiitis, Churg–Strauss syndrome) showed a slight increase, with an annual incidence of 19.8/million [7]. Unpublished data from our registry suggest that the incidence of PSV over the last 5 yr has been stable, again suggesting that the decrease in SRV is not an artefact. Possible explanations for the observed decline in SRV include the increased use of methotrexate and other immunosuppressive agents together with improved strategies to control inflammatory burden, and changes in smoking habits. Methotrexate has widely been used in patients with RA in Norfolk only since 1988, and more recently in early disease. Patients presenting in the 1990s would be more likely to have received methotrexate earlier in their disease course than patients diagnosed in the 1980s. Oral corticosteroids have been identified as a risk factor for development of SRV [14]. Unfortunately, our database does not permit us to examine the exact dose and timing of methotrexate or corticosteroid usage in our patients. Smoking is known to be a risk factor for the development of extra-articular disease [12] and for peripheral vascular disease in general. Smoking has declined in England over the past 30 yr and this may be a factor in the decline in SRV.

A formal case-control study is required to assess whether changes in drug use and disease control are responsible for the decline in SRV seen in our population over the last 15 yr.

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References