Development of diagnostic criteria sets for systemic vasculitis

Project description

Background
The primary systemic vasculitides are an important cause of mortality and morbidity in the community. Their incidence is greater than 100 new cases per million per year (1). Initial reports of therapy have shown significant benefit with intensive chemotherapy but if the diagnosis is delayed then subsequent outcome may become significantly affected. It is suggested that up to 25% of patients on chronic haemodialysis programmes have had undiagnosed systemic vasculitis as a major contributor to renal failure (2).

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 or without a specific disease, diagnostic criteria are required. There are currently no validated diagnostic criteria for primary systemic vasculitis although the existing classification criteria (3) and disease definitions (4) have been misapplied. When tested, the CHCC definitions supplemented with surrogate clinical and laboratory parameters failed to act as diagnostic criteria (5).

Diagnostic criteria for primary systemic vasculitis would be most useful for practising clinicians who could rapidly and accurately assess the probability of vasculitis in the context of patients who present to them acutely, especially those with multi-system illnesses. There are currently no satisfactory serological tests to enable a rapid diagnosis of vasculitis. We have shown that in non-specialised hands, an ANCA test (by indirect immunofluorescence) has a diagnostic yield of 0-12% for systemic vasculitis (6).

We are currently revising existing classification criteria for systemic vasculitis, in a combined EULAR/ACR taskforce (due to report in early 2009). In the combined project we will develop a revision of the ACR (1990) criteria and incorporate disease definitions, based on the Chapel Hill consensus definitions (Jennette et al 1994) for systemic vasculitis; we will also develop proposed diagnostic criteria, which will require validation [1, 2]. As well as revising the existing ACR (1990) criteria [2-10], we need to create new criteria for microscopic polyangitis (MPA), this in turn requires a re-definition of classical polyarteritis nodosa; we need to review the definition and criteria for cryoglobulinaemic vasculitis as a result of the evidence linking it to hepatitis C in most cases. The criteria and definitions of cutaneous vasculitis need to be reassessed in line with current understanding of their pathogenesis. We need better definitions of early undifferentiated vasculitis, unclassified and unclassifiable vasculitis. For each disease we will develop a comprehensive list of potential items (content validity) to serve as classification or diagnostic criteria.

Current proposal
We propose to develop diagnostic criteria for patients presenting with multi-organ disease. An important aspect of this study is the disease controls e.g. systemic lupus erythematosus, infection, who have a vasculitis-like presentation. We will evaluate patients who present with potential vasculitis to determine the usefulness of clinical criteria and serological parameters in distinguishing those patients who are subsequently recognised as having systemic vasculitis. It is only in this context specific setting that we can determine the true usefulness of our diagnostic criteria. We will also recruit cases with known vasculitis, assessing disease activity and severity using the Birmingham Vasculitis Activity Score [11], so that we can assess the value of criteria in a predefined population of patients with diagnosed vasculitis. We will assess the reproducibility, redundancy of items, clinical relevance and ease of use of each set of criteria. An initial power calculation, based on pilot data (12) suggests that we would need to recruit 100 new cases for each condition, 100 existing cases for each condition and a total of 2000 controls, hence the requirement for 30 centres. For the individual criteria and combinations of criteria we will determine the sensitivity and specificity. We will identify those criteria with the greatest content and construct validity by a Delphi exercise within the members of the group. We will follow the ACR recommended statistical methods for creating the diagnostic and classification criteria [12, 13].
**Patient evaluation – entry**
For each case or disease control, new patients will be evaluated within 10 days of the onset of their presentation to hospital; existing vasculitis patients will be recruited during normal clinic attendances. For each patient or control, the following will be recorded as a minimum routine dataset: presence of classification and diagnostic criteria as defined in the ACR/EULAR criteria set; BVAS (without attribution to disease activity); ANCA (samples sent to single reference laboratory for analysis); CRP (or ESR / PV); Blood pressure; Serum creatinine; Urinalysis and urine microscopy; chest radiograph.

**Patient evaluation - follow up**
For new cases, the consensus clinical diagnosis (made by the patient’s attending physician and corroborated by the study investigators) at 6 months follow up will be recorded. Slides will be scored blind to other patient data by two observers (Prof. Charles Jennette and Dr Ingeborg Bajema). Positive evidence of other disease processes and or lack of evidence of vasculitis based on appropriate investigations e.g. histology, serology, radiology etc. will be recorded in the remaining patients.

**Recruitment**
We anticipate recruitment of about 10 patients per month who might have vasculitis (or a vasculitic mimic condition), and a further 2-3 per month with definite vasculitis for 12 months totalling 120 new patients per annum per centre (3600 patients per annum, including 360 with new vasculitis per annum) and 30 patients with existing vasculitis per annum per centre (900 patients per annum). We assume a 10% loss to follow up rate inclusive of patients who have declined consent to take part in the study. The remaining patients will be entered into the study. Using the pulmonary renal syndrome as an example, data from Westman et al. showed that 11% of patients in this context were found to have systemic vasculitis. We assume that around 10% of our patients will have a subsequent diagnosis of vasculitis. We will evaluate the use of linear logistic regression models in an attempt to determine the diagnostic value of individual criteria within each clinical context. We will look at factors univariately and examine correlations between variables using linear logistic regression models in an exploratory way.

**Justification of need for project**
The current ACR (1990) classification criteria for systemic vasculitis were developed from large retrospective cohorts of patients with 7 forms of vasculitis (Giant cell arteritis (GCA), Takayasu arteritis (TA), Wegener’s granulomatosis (WG), Churg Strauss syndrome (CSS), polyarteritis nodosa (PAN), Henoch Schönlein purpura (HSP) and hypersensitivity vasculitis (HSV)) plus a separate classification of unspecified vasculitides. The sensitivity and specificity vary between 71.0-93.5% and 83.9-99.7% respectively. However, the criteria have not been widely validated in a prospective cohort, and never tested Subsequent to the development of the criteria and particularly following the development of the Chapel Hill Consensus Definitions in 1994 [14] it has become apparent that the criteria need to be updated. In particular the recognition of microscopic polyangiitis (MPA) as a discrete condition and the introduction of the anti-neutrophil cytoplasmic antibody (ANCA) test mean that the criteria need revision.

This will build on the work started by the collaborative EULAR/ACR group considering ‘EULAR/ACR endorsed points to consider in the diagnosis of the systemic vasculitides’. Preliminary data from a survey of the members of this group (21 international experts in the field of vasculitis) who were asked ‘are the current ACR criteria fit for purpose?’ shows that 85% felt that the criteria for WG and HSP were currently not fit for purpose, and 76% felt the criteria for CSS, PAN and HSV were unfit. The criteria for GCA and TA were felt to be unfit by 38% and 43% respectively (Basu, Watts, Luqmani unpublished data). Content validity was felt to be poor particularly the lack of inclusion of ANCA. New criteria were required for consistency with the CHCC definitions and the division of PAN into MPA and classical PAN as suggested by the CHCC.

Furthermore there are no validated diagnostic criteria for the systemic vasculitides. The ACR (1990) criteria are often used incorrectly as diagnostic criteria and they have been shown to perform badly when used for that purpose.[15]
We therefore feel that the time is right for a revision of the ACR criteria for vasculitis to bring make them relevant for the 21st century and to develop for the first time a set of validated diagnostic criteria.

Suggested PIs
The suggested PIs for the project are: Dr Richard Watts (University of East Anglia, Norwich, UK), Dr Raashid Luqmani (University of Oxford, Oxford, UK), Dr Peter Merkel (Boston University School of Medicine, Boston, USA). Drs Watts and Luqmani also represent the European Vasculitis Study Group (EUVAS) group. The PIs represent 3 recruiting centres.

Suggested collaborators
The systemic vasculitides are multisystem diseases and therefore to ensure that the criteria developed adopted by the vasculitis community in general we have included members from other relevant disciplines and from a broad range of countries.

US members including 7 recruiting centres:

- Professor Len Calabrese, Cleveland, USA (Rheumatologist)
- Dr John Davis UCLA USA (Rheumatologist)
- Professor Ron Falk, Chapel Hill, USA (Nephrologist)
- Professor Charles Jennette, Chapel Hill, USA (Pathologist)
- Dr Carol Langford Cleveland USA (Rheumatologist)
- Professor Eric Matteson, Mayo Clinic, Rochester Minnesota USA (Rheumatologist)
- Dr Robert Spiera, New York USA (Rheumatologist)

European members including 17 recruiting centres:

- Dr Ingeborg Bajema, Leiden, The Netherlands (Pathologist)
- Dr Maria Cid, Barcelona, Spain (Rheumatologist)
- Dr Kirsten de Groot, Hanover, Germany (Nephrologist)
- Professor Wolfgang Gross, Bad Bramstedt, Germany (Rheumatologist)
- Professor Loic Guillevin, Paris, France (Internal Medicine)
- Dr Thomas Hauser, Zurich, Switzerland (Immunologist)
- Professor Cees Kallenberg, Groningen, The Netherlands (Immunologist)
- Dr David Jayne, Cambridge, UK (Nephrology)
- Dr Niels Rasmussen, Copenhagen, Denmark (ENT Surgeon)
- Dr Carlo Salvarani, Reggio Emilia, Italy (Rheumatologist)
- Dr Alan Salama London UK (Nephrology)
- Professor Caroline Savage, Birmingham, UK (Nephrologist)
- Professor David Scott, Norwich, UK (Rheumatologist)
- Professor Marten Segelmark, Lund, Sweden (Nephrologist)
- Professor Cord Sundercotton, Munster, Germany (Dermatologist)
- Professor Jan Wilhelm Cohen Tervaert, Maastricht, The Netherlands. (Immunologist)
- Professor Vladimir Tesar, Prague, Czech Republic (Nephrologist)
- Professor Hasan Yazici, Istanbul, Turkey (Rheumatologist)

Mexico

- Dr Luis Felipe Flores Suarez (Rheumatologist)

Japanese members:

- Professor Kazuo Suzuki, Tokyo, Japan (Internal Medicine)
- Dr Shigeto Kobayashi, Tokyo, Japan (Rheumatologist – Co-ordinator Japan/EUVAS study group)

Project Statistician:
Professor Maarten Boers Amsterdam Nethrelands (Rheumatologist)

Opportunities for trainee involvement:
These include developing a greater understanding of how vasculitis presents, and how to distinguish it from other conditions such as infection; recruitment of patients and assisting with data analysis. A current trainee has coordinated the current EULAR/ACR project.

References