Antineutrophil cytoplasmic antibodies and the eosinophilia myalgia syndrome

The eosinophilia myalgia syndrome (EMS) is an inflammatory multisystem disease which emerged in epidemic form in 1989 and was linked to the ingestion of L-tryptophan. In the acute form of the EMS, severe myalgia and pronounced blood eosinophilia are accompanied by widespread fever, skin rash, and neurological complications. The chronic form of the EMS is characterised by progressive myalgia, fatigue, and unaesthetic eosinophilic fascitis, accompanied by polyneuropathy, chronic fatigue, and psychosomatic dysfunction.

A spectrum of vascular lesions has been described including perivascular and interstitial alterations of the vascular endothelium, and frank vasculitis with mural infiltration by mononuclear cells. The last of these was found primarily in small arteries, veins and capillaries, and by immunofluorescence microscopy no deposition of immunoglobulins or complement components was found.

These histopathological features resemble those of the pauci-immune small vessel vasculitides, a group of diseases strongly associated with antineutrophil cytoplasmic antibodies (ANCAs). In the March 1991 issue of this journal Cilurzo and colleagues reported a patient with acute EMS and perinuclear ANCA (pANCA) with anti-myeloperoxidase (MPO) specificity together with a small vessel vasculitis in skeletal muscle. This report prompted the question whether EMS also is an ANCA associated disease.

From a nationwide collection of EMS sera, we tested a random sample of 45 sera for ANCA. The sera were from 39 females (age 30–69 years) and six males (age 51–61 years) who fulfilled the diagnostic criteria of chronic EMS. ANCA testing was performed in compliance with the guidelines of the European ANCA Study Group with an indirect immunofluorescence test on ethanol fixed and formalin fixed granulocytes; antibody specificity was tested by specific enzyme linked immunosorbent assay (ELISA) using proteinase 3 (PR3), MPO, lactoferrin, lysozyme, elastase, and cathepsin G as antigens. For distinction between pANCA and antinuclear antibodies (ANA), sera were also examined on cultured human cells.

We found none of the 45 sera to be positive for ANCA. Likewise all sera were negative by ELISA testing for the above mentioned antibody specificities. A number of sera produced fluorescent staining on the alcohol fixed granulocytes; however, this was attributable to ANA. In a Chag cell assay, 19 of 45 sera (42%) tested positive for ANA.

The strongest clinical associations of ANCA have been shown to be that of anti-PR3 with Wegener's granulomatosis (WG) and of anti-MPO with microscopic polyangiitis (MPA) and pauci-immune rapidly progressive glomerulonephritis (RPGN). These disorders have been categorised as the ANCA-associated vasculitides. In WG, 80% of patients are positive for cytoplasmatic ANCA (cANCA); in generalised disease this is the case in more than 90%, with anti-PR3 being the most frequent antibody sub specificity (table). The association between pANCA or anti-MPO and MPA or pauci-immune RPGN is less strong—approximately 65% of MPA patients are anti-MPO-positive. While anti-PR3 is highly specific for WG, anti-MPO has also been found at a low rate and in low titers in a number of other chronic inflammatory diseases.

A strong association of ANCA with secondary vasculitis has not yet been found. The present results confirm with this; notably, no serum showed anti-PR3 or anti-MPO reactivity. These results thus add to the evidence that anti-PR3 and anti-MPO are important markers for the classification and clinical diagnosis of primary systemic vasculitides, but not secondary vasculitides. The low prevalence of ANCA in the EMS makes it unlikely that ANCA have a pathogenetic role in this disorder.

Clinical associations of antineutrophil cytoplasmic antibodies (ANCA)

<table>
<thead>
<tr>
<th>ANCA</th>
<th>anti-PR3</th>
<th>pANCA</th>
<th>anti-MPO</th>
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</thead>
<tbody>
<tr>
<td>18%</td>
<td>38% (80%)</td>
<td>5 (1%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>8 (18%)</td>
<td>3 (7%)</td>
<td>33 (72%)</td>
<td>28 (64%)</td>
</tr>
<tr>
<td>15 (30%)</td>
<td>5 (12%)</td>
<td>16 (32%)</td>
<td>16 (32%)</td>
</tr>
</tbody>
</table>

Correspondence to: Dr A Schnabel.

9 Hagen E C, Andressy K, Csernok E, et al. The histological findings of specific heart involvement. A strong association of ANCA with secondary vasculitis has not yet been found. The present results confirm with this; notably, no serum showed anti-PR3 or anti-MPO reactivity. These results thus add to the evidence that anti-PR3 and anti-MPO are important markers for the classification and clinical diagnosis of primary systemic vasculitides, but not secondary vasculitides. The low prevalence of ANCA in the EMS makes it unlikely that ANCA have a pathogenetic role in this disorder.

Silent myocardial infarction in Wegener’s granulomatosis

At postmortem, patients with Wegener’s granulomatosis (WG) frequently show a clinically overlooked and diffuse disease process. Cardiologically, many such patients have been asymptomatic but present histological findings of specific heart involvement. We report two cases of silent myocardial infarction related to WG—a feature which, to our knowledge, has not been reported in clinical series.

Patient 1. A 42 year old man was admitted to hospital because of severe vasculitis flare. He had an eight month history of arthritis and lower limb dysaesthesia. Examination showed an acutely ill patient with a 39°C fever. He had oral ulcers, haemorrhagic gingival hyperplasia, bilateral haemorrhagic nasal discharge with crusts, diffuse necrotic purpura and black discoloration of fingers and toes. Ankle jerks were absent. Standard blood tests showed: leucocyte count 9.6 x 10^9/l; serum creatinine 112 µmol/l; C reactive protein 278 mg/l; fibrin 12 g/l; total creatine kinase (CK) concentration 1102 U (normal range 15–60 U). Serology: Eosinophilic infiltration, CD 10, CD 68, and CD 45. In the immunophenotypic studies of the eosinophilic myalgia syndrome, 1/3 of the patients were positive for ANCA. The results thus add to the evidence that anti-PR3 and anti-MPO are important markers for the classification and clinical diagnosis of primary systemic vasculitides, but not secondary vasculitides. The low prevalence of ANCA in the EMS makes it unlikely that ANCA have a pathogenetic role in this disorder.
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A Schnabel, W L Gross, P A Berg, R Klein and H Lehnert

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