Letters to the Editor

Fatigue in rheumatoid arthritis

Sir, We write in response to an editorial in Rheumatology defining what is known and what remains to be learned about fatigue in RA [1]. Repping-Wuts et al. [1] recognize fatigue as a common and severe complaint, having a major impact on the quality of life in patients with RA. They emphasize that doctors often underestimate this effect and also that the issue is usually raised by patients rather than by health care professionals. We agree with this and welcome the suggestion that a more proactive approach to the identification and management of fatigue in RA is necessary. However, it is important that fatigue is not assumed to be secondary to RA in isolation. Other potentially treatable contributory conditions should be actively sought. Anaemia is frequently associated with RA and often presents with fatigue. Hypothyroidism is also common in patients with RA, usually as a result of autoimmune disease, and symptoms may include fatigue. Most rheumatologists would recognize these associations and check a full blood count and thyroid stimulating hormone in an RA patient with such symptoms.

We recently investigated fatigue in our RA population by checking random cortisol levels in 50 patients who complained of excessive fatigue, and in whom anaemia and hypothyroidism had already been excluded. We performed a Synacthen test in the eight patients whose results were low (<200 nmol). This was normal, excluding hypoadrenalism, in four. Two further patients had a blunted response as a result of previous long-term oral steroid therapy producing inhibition of adrenal response. The two remaining patients had little response to ACTH, with high circulating ACTH levels and anti-adrenal antibodies. Baseline cortisol levels were 26 and 51 nmol, rising 30 min after ACTH to just 112 and 120 nmol, respectively. These two patients had primary adrenal failure (Addison's disease) of autoimmune aetiology. They subsequently responded well to physiological doses of hydrocortisone. Ethical approval for the study was provided by the Northern Regional Ethical Committee.

Clearly our data do not allow any firm conclusions to be drawn about the prevalence of Addisons disease in RA. However, it is feasible that autoimmune adrenalitis may be more common in RA than in the population at large [2]. Certainly an association between Addisons disease and other chronic disorders has been demonstrated, with the authors postulating links through autoimmunity [3]. We suggest that fatigue in patients with RA, in addition to being a feature of that disease, might represent coexisting physical disorders relating to other autoimmune processes. Before assigning such symptoms to RA itself, clinicians may be well advised to check thyroid function and cortisol levels. Such a strategy should sensibly preface the introduction of oral steroids.

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Efficacy of rituximab in refractory and relapsing myositis with anti-JO1 antibodies: a report of two cases

Sir, The anti-Jo1 (histidyl tRNA synthetase) antibodies are often associated with myositis, arthritis, RP, mechanic's hand and interstitial lung disease (ILD), the latter governing the prognosis of this anti-synthetase syndrome. A 49-year-old woman presented marked muscular weakness (psoas and deltoids MRC 3/5, legs held outstretched at 45° supine: 22 s, normal >75 s) with anti-Jo1 antibodies. Creatine kinase (CK) level was 1114 U/l with anti-Jo1 antibodies. Creatine kinase (CK) level was 1114 U/l. Muscle biopsy confirmed myositis. CT scan was normal. The patient was treated with prednisone 1 mg/kg/day (60 mg/day) associated with AZA (150 mg/day). Three months later, she improved (psoas and deltoids MRC 4/5, legs outstretched at 45° supine: >75 s) with normalization of CK levels. At 12 mg/day of prednisone (after 20 months), she relapsed with muscle weakness (psoas and deltoids MRC 3/5, legs outstretched at 45° supine: >75 s) and increased CK levels (1018 U/l) leading to introduce monthly high-dose (2 g/kg) intravenous immunoglobulins (IVIgs) and oral daily mephenyl- late mofetil (MMF, 2 g/day). However, after nine courses of IVIg, weakness progressed (psoas and deltoids MRC 3/5, legs outstretched at 45° supine: >75 s) and CK continued to rise (3296 U/l). We decided to then use rituximab (2 x 1 g, 2 weeks apart), while increasing prednisone to 1 mg/kg/day and maintaining MMF. A third injection of rituximab (1 g) was performed 6 months later. The patient showed then total recovery with normal muscle strength, normal CK level, allowing to taper corticosteroid doses at 10 mg/day and to stop MMF. Ten months after the third injection of rituximab, she exhibited a further relapse with polyarthralgia, proximal muscle weakness (psoas MRC 3/5 and deltoid MRC 4/5, legs outstretched at 45° supine: 26 s) and CK levels at 4863 U/l. She then received again rituximab (1 g 2 weeks apart). Six months later, symptoms disappeared and CK decreased to 150 U/l.

A 19-year-old woman presented with proximal muscle weakness (psoas and deltoids MRC 4/5, legs outstretched at 45° supine: 70 s) with anti-Jo1 antibodies. CK level was 11 990 U/l. Muscle biopsy confirmed myositis. CT scan revealed ILD. Prednisone 1 mg/kg/day associated with MMF (2 g/day) were started with a
TABLE 1. Characteristics of 10 patients with anti-synthetase syndrome (all are anti-Jo1+) treated by rituximab

<table>
<thead>
<tr>
<th>References</th>
<th>Age, years/sex</th>
<th>Clinical features</th>
<th>Pulmonary parameters</th>
<th>Baseline CK level, U/l</th>
<th>Previous treatment, duration, months</th>
<th>Rituximab regimen</th>
<th>Outcomes (relapse)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brulhart et al. [1]</td>
<td>57/F A, MH, PMW and D</td>
<td>Mild ILD in lower lobes CODC: 72%</td>
<td>8274</td>
<td>Pred, MTX, 5</td>
<td>2 × 1 g</td>
<td>Increasing strength Normalization of CK level Disappearance of lung abnormalities (Yes at 8 months)</td>
<td></td>
</tr>
<tr>
<td>Gottenberg et al. [2]</td>
<td>53/F PMW</td>
<td>NA</td>
<td>1364</td>
<td>Pred, MTX, AZA, IVlg, 72</td>
<td>4 × 375 mg/m²</td>
<td>Increasing strength Normalization of CK level (No at 4 months)</td>
<td></td>
</tr>
<tr>
<td>Lambotte et al. [3]</td>
<td>55/F PMW Pemphigus</td>
<td>NA</td>
<td>252</td>
<td>Pred, ALC, HCO, IVlg, MTX, 228</td>
<td>4 × 375 mg/m²</td>
<td>Increasing strength Normalization of CK level (Yes at 4 months)</td>
<td></td>
</tr>
<tr>
<td>Sultan et al. [4]</td>
<td>47/F PA, MH, PMW</td>
<td>ILD CODC/AV: 74%</td>
<td>136</td>
<td>Pred, MTX, AZA, IVlg, 60</td>
<td>4 × 375 mg/m²</td>
<td>Increasing strength Normalization of CK level CODC/AV: 93% (No at 12 months)</td>
<td></td>
</tr>
<tr>
<td>Vandenbroucke et al. [5]</td>
<td>56/F PMW</td>
<td>ILD</td>
<td>610</td>
<td>Pred, MTX, IVlg, Csf, Lef, P, Embrel, 168</td>
<td>2 × 1 g at 18 months</td>
<td>Increasing strength Normalization of CK level (Yes at 10 months)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>63/F PMW</td>
<td>ILD FVC: 50% DLOCO: 41%</td>
<td>400</td>
<td>Pred, AAZA, 72</td>
<td>2 × 1 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57/F PMW</td>
<td>NA</td>
<td>1571</td>
<td>Pred, MTX, Cs, AZA</td>
<td>2 × 1 g</td>
<td>Non-responder Subsequently diagnosed with lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48/M D, A, PMW</td>
<td>ILD FVC: 55% FEV1: 58%</td>
<td>718</td>
<td>Pred, CyP, 2</td>
<td>2 × 1 g</td>
<td>Increasing strength Normalization of CK level Less ground glass on CT scan and stabilization of fibrosis (No at 3 months)</td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>49/F PA, MH, PMW, RP</td>
<td></td>
<td>1114</td>
<td>Pred, AZA, MMF, IVlg, 34</td>
<td>2 × 1 g at 6 months</td>
<td>Increasing strength Normalization of CK level (Yes at 16 months)</td>
<td></td>
</tr>
<tr>
<td>Case 2</td>
<td>19/F PA, PMW, D</td>
<td>ILD, CODC: 51%</td>
<td>11990</td>
<td>Pred, MMF, AZA, 7</td>
<td>2 × 1 g at 17 months</td>
<td>Increasing strength Normalization of CK level Less ground glass on CT scan (Yes at 14 months)</td>
<td></td>
</tr>
</tbody>
</table>

F: female; M: male; A: arthritis; PA: polyarthralgia; MH: mechanic’s hand; PMW: proximal muscle weakness; D: dyspnea; CODC: CO diffusion capacity; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; AV: alveolar volume; Pred: prednisone; CyP: cyclophosphamide; Cs: cyclosporine; P: penicillamine; ALC: alchoyline; MMF: mycophenolate mofetil; NA: not available.

Rituximab can be effective (but transiently) for the treatment of anti-Jo1 myositis.

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Catastrophic anti-phospholipid syndrome associated with Escherichia coli O157 infection

Sin, Catastrophic APS (CAPS) is a term applied to aPL-mediated disorder in which multiple thrombi of small vessels affect the viscera over a relatively short period [1–3]. CAPS is rare in children and may be confused with haemolytic-uraemic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP) because of similar clinical manifestations. More importantly, it will be easily overlooked if associated with an acute episode of HUS/TTP itself. We describe the case of a 9-year-old girl with haemorrhagic colitis caused by Escherichia coli O157 who developed CAPS during the course of her disease.

A 9-year-old girl with a 4-day history of fever, bloody diarrhoea and abdominal pain was transferred to our department because of suspected HUS after continued elevation of urea and creatinine levels despite adequate resuscitation. On examination, she had no fever, her heart rate was 88 b.p.m., and her blood pressure was 80/40 mmHg. She had no purpura or oedema. Her consciousness was clear, and neurological examination was normal. Laboratory examinations showed increased CRP levels, 3.2 mg/dl; white blood cell count, 13.52 × 10^9/l; haemoglobin, 12.3 g/dl; platelet count, 40 × 10^9/l; signs of haemolysis with positive fragmented red cells in the blood smear; and elevated lactate dehydrogenase levels, 3474 IU/l. Liver and kidney function tests showed elevated urea (47 mg/dl), creatinine (3.87 mg/dl), aspartate aminotransferase (281 IU/l) and bilirubin (3.2 mg/dl) levels. Coagulation tests showed prolonged prothrombin time (15.1 s), increased fibrinogen degradation products (32.3 μg/ml) and increased d-dimer levels (10.5 μg/ml). Activated partial thromboplastin time and fibrinogen were normal. Stool culture and toxin assays for Shiga-like toxin were negative but O157 LPS antibody was positive, thus confirming infection with enterohaemorrhagic E. coli. The patient rapidly progressed to anuria and required placement of a dialysis catheter and initiation of haemodialysis. Haemodialysis improved her renal function; it was stopped on the ninth day after admission. Immunoserological testing on the 10th day after admission showed a positive level of IgG aCL (14.2; <10 U/ml; ELISA), IgG phosphatidylserine-dependent prothrombin antibody (aPS/PT) (25; <10 U/ml; ELISA) and IgM aPS/PT (37; <10 U/ml; ELISA). IgG β2-glycoprotein I (β2GPI)-dependent aCLs and lupus anti-coagulant were negative. ANA was positive (30.7; index <20; ELISA). Other autoantibody tests, including RF, anti-ssDNA antibody, anti-dsDNA antibody and MPO-ANCA, were negative. The plasma level of ADAMTS-13 activity was slightly decreased to 15%, but the von Willebrand factor multimeric pattern was normal. A kidney biopsy performed on the 19th day after admission showed a typical histopathological picture of thrombotic microangiopathy (TMA) and no immune deposits (Fig. 1). Brain MRIs were normal. Radioisotope venography revealed left deep-vein thrombosis. The patient fulfilled the classification criteria for CAPS [3]. She received anti-coagulation therapy and was in clinical remission for 16 months.

Escherichia coli O157 is one of the most popular pathogens causing HUS. However, enteropathogenic E. coli has not been recognized as an infectious agent that triggers CAPS. To our knowledge, this is the first report of CAPS caused by E. coli O157 infection.

There are reports of a high frequency of aCL in children with diarrhoea-associated HUS [4, 5]. Ardiles et al. [4] found a positive aCL in 59% (10/17) of the patients with classic HUS, without correlation with clinical variables. Furthermore, Te Loo et al. [5] reported a significant increase in aCL levels during the acute phase of diarrhoea-associated HUS; IgM aCL was positive in 60% and IgG aCL in 41% of patients. A new subset of APS, termed microangiopathic APS (MAPS), was recently proposed. MAPS comprises those patients with TMA such as HUS/TTP, haemolysis, elevated liver enzymes, and low platelets syndrome and demonstrable aPL [6]. The aPL detected in this group of patients may be generated by endothelial damage or preceding infection [7]. Some of these non-pathogenic aPL may be rendered pathogenic by unknown factors in these conditions. However, we hypothesize that in some patients with HUS/TTP, the circulating aPL may contribute as a concomitant prothrombotic risk factor to the microvascular thrombotic process. The pathogenic role of aPL in clinical conditions of patients with TMA remains controversial; however, aPL should be examined in patients with TMA because anti-coagulant treatment is necessary in APS, particularly in CAPS.

aPS/PT was highly prevalent in patients with APS compared with patients with other diseases, and the detection of aPS/PT...