MATTERS ARISING

Pulsed electromagnetic field therapy in the management of knee OA

It seems most unusual that in a review of “all currently available treatments” for knee osteoarthritis (OA) by 21 authorities and “two experts in the field of guidelines methodology”, pulsed electromagnetic field therapy was not mentioned in the text or the 51 references. This is particularly troubling because over 2800 publications between 1966 and 1998 were retrieved. An identical search for efficacy of magnetic field therapy during this period listed 51 studies with at least one control group, including two double blind trials citing benefits in knee OA from a peer reviewed arthritis journal. In 1999 over 50 000 patients received pulsed signal therapy (PST) prescribed by over 1000 doctors at more than 300 clinics and hospitals in 16 countries, where it is usually reimbursed by fiscal intermediaries because of its proven record of cost effectiveness and safety. A summary of PST double blind and randomised study results in over 50 000 patients has been published, and findings in 100 000 patients (the vast majority with knee OA) have also been reported at recent international conferences. Although “alternative” remedies, ranging from minerals, vitamins, nutritional supplements, and caspacin and diclofenac gels to sex hormones were discussed, in contrast with PST, none satisfied the category criteria the panel established to determine strong recommendation. Nor do any have the solid basic science studies that PST provides with its in vitro support for mechanisms of action to explain efficacy based on proteoglycan synthesis and chondrocyte regulation results.

Pulsed signal therapy is the result of three decades of research designed to characterise the piezoelectric signal that normally stimulates chondrocyte activity by creating a streaming potential in the extracellular matrix when bone is subjected to pressure. Although the transmission of this signal is impaired in OA, PST can reproduce this streaming potential in a matrix when bone is subjected to pressure. The measurement of anti-factor Xa activity in plasma enables us to calculate the dose of low molecular weight heparin which is needed to achieve optimal inhibition of the coagulation cascade. Values of 0.6–1.0 U/ml are usually believed to give maximum protection against thromboembolic events. From my experience the optimal dose of low molecular weight heparin which is needed to achieve optimal inhibition of the coagulation cascade. Values of 0.6–1.0 U/ml may be different in different patients. Moreover, a second injection has to be applied to achieve effective. Therefore, as long as controlled data are missing I would suggest that the measurement of anti-factor Xa activity in pregnant patients with APS should be used to adjust the dose of low molecular weight heparin. This may result in better protection of mother and fetus in this disease.

I read with much interest the article of Berk et al in the January issue of the Annals of the Rheumatic Diseases. The authors gave a detailed introduction to the clinical effect of treatment of pregnant patients with antiphospholipid syndrome (APS). Despite the presence of only a limited amount of data from controlled studies the authors gave helpful recommendations for the daily management of these patients.

However, there is a major concern with which I would like to deal. As we know the success of treatment of APS with oral anticoagulants very much depends on the strictness with which the dose is adjusted to the international normalised ratio. The authors rightly suggest changing from oral anticoagulants to subcutaneous low molecular weight heparin in pregnant patients with APS. However, I believe that the dose of low molecular weight heparin has to be adjusted in individual patients.

The measurement of anti-factor Xa activity in plasma enables us to calculate the dose of low molecular weight heparin which is needed to achieve optimal inhibition of the coagulation cascade. Values of 0.6–1.0 U/ml are believed to give maximum protection against thromboembolic events.

Although I am certified in cardiology and gastroenterology, a significant portion of my practice is now devoted to exploring how PST achieves its benefits. I have treated 1000 patients, most of whom had knee OA, with very gratifying results similar to those reported in the literature. The panel cited two prior efforts to establish guidelines for treating knee OA, emphasising that these “primarily represent consensus statements from expert panels” and “the type and strength of evidence to support such guidelines remain unclear.” Their stated objective, therefore, was to “develop guidelines relating to clinical issues in OA management, and to indicate clearly the level of evidence to support individual statements”. However, electromagnetic therapy approaches were again omitted, though at least one of the members is quite familiar with PST. The reason for this exclusion is not clear and I believe that your readership deserves to be aware of this extremely safe and effective option.

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Pulsed electromagnetic field therapy, with other less commonly used interventions, was not included in this list, and its evidence for efficacy was therefore not assessed. However, as emphasised by Dr Pfeifer, an evidence-based evaluation of all other interventions would be of interest and could be considered for inclusion in the next round of evidence based guidelines.

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Treatment of women with aPL in pregnancy

I read with much interest the article of Derkx et al in the January issue of the Annals of the Rheumatic Diseases. The authors gave a detailed introduction to the clinical effect of treatment of pregnant patients with antiphospholipid syndrome (APS). Despite the presence of only a limited amount of data from controlled studies the authors gave helpful recommendations for the daily management of these patients.

However, there is a major concern with which I would like to deal. As we know the success of treatment of APS with oral anticoagulants very much depends on the strictness with which the dose is adjusted to the international normalised ratio. The authors rightly suggest changing from oral anticoagulants to subcutaneous low molecular weight heparin in pregnant patients with APS. However, I believe that the dose of low molecular weight heparin has to be adjusted in individual patients.

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From my experience the optimal dose of low molecular weight heparin which is needed to achieve optimal inhibition of the coagulation cascade. Values of 0.6–1.0 U/ml may be different in different patients. Moreover, a second injection has to be applied to achieve effective. Therefore, as long as controlled data are missing I would suggest that the measurement of anti-factor Xa activity in pregnant patients with APS should be used to adjust the dose of low molecular weight heparin. This may result in better protection of mother and fetus in this disease.

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Caudal epidural injections

Price et al recommend that caudal epidural injections should be carried out with x-ray screening. In practice the technique of screening is not usually available.

Interleukin 1 gene polymorphisms

I read with interest the recent article by Crilly and colleagues' on the potential use of interleukin 1 (IL1) gene polymorphisms in predicting the need for joint surgery in patients with rheumatoid arthritis. Although the authors' findings are certainly interesting and worthy of further investigation, I would like to raise a couple of points as to how these were arrived at in the first place.

When adopting the "candidate gene" approach in any disease association study, it pays to consider carefully the physiological context of a hypothesis. In this case the authors worked on the premise that one of the IL1 gene family polymorphisms might correlate with disease outcome. These included polymorphisms both in the IL1 genes and the IL1 receptor antagonist (IL1ra) locus. The IL1ra is unique in being the only known endogenous cytokine receptor antagonist. The genes encoding IL1α, β...
and the IL1ra have co-evolved as a cytokine control mechanism: agents eliciting IL1 production generally induce IL1ra gene transcription as well, either directly or through a feedback loop triggered by IL1 itself. IL1ra competes with IL1 for binding to the cognate receptor, but produces no known signalling events upon binding. Additionally, one of the two IL1 receptors, type II, also lacks any known signalling capacity and is thought to function as a decoy binding site. If it is assumed that polymorphisms found in various members of the IL1 gene family modify gene function then the implication is that they should be studied collectively, not individually. In support of this argument comes recent experimental evidence showing that the IL1a-IIa receptors are determined free from allelic combinations within the IL1 gene family, as well as evidence for linkage disequilibrium between polymorphic markers spread across the IL1 gene family locus. It is fair to say that Crilly and colleagues did allude in their paper to the possible existence of a 15 year disease duration free from surgery inflammation, or mechanical nerve compression. The wrist joint was injected with 20 mg of triamcinolone acetate with 1% lidocaine (lignocaine). The erythrocyte sedimentation rate (ESR) was raised at 73 mm/1st h. A transcutaneous nerve-stimulating (TENS) machine was applied and she was prescribed amitriptyline 25 mg at night. The following day she had received acyclovir early to avoid viral dissemination. In patients with RA the complexity of the differential diagnosis may delay diagnosis unless the possibility of herpes zoster infection is kept in mind. Conflict of interest: none.

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fevers, gastrointestinal disturbances of nausea and vomiting, granulocytopenia, and hepato-cellular injury. More rarely, hypersensitivity can present with features of severe systemic infection and end organ dysfunction. Azathioprine is a commonly used immunosuppressive drug and is used in many medical specialties. Therefore recognising azathioprine hypersensitivity is important for all doctors. We report a case in which we suspect such an azathioprine hypersensitivity reaction.

A 32 year old Asian woman with mixed connective tissue disorder presented with a one day history of general malaise, fevers, and painful digits. Fourteen days earlier treatment had been started with azathioprine 50 mg daily, and her prednisolone increased from 5 mg to 15 mg daily owing to the development of proteinuria (1.5 g on 24 hour urine collection) and urticarial vasculitis on her lower legs.

On examination she was shocked, with a blood pressure of 70/30 mm Hg and had marked acrocyanosis (fig 1). The differential diagnosis included a lupus crisis or septic shock. She was treated in the intensive care unit with intravenous ceftriaxone, metronidazole, and prostacyclin for digital ischaemia after serial cultures were taken from all major sites. Staphylococcal toxic shock was excluded, with no growth on vaginal swabs and a negative staphylococcal toxin test. After negative cultures 1 g methylprednisolone was given for a possible flare up of her connective tissue disease. The azathioprine was discontinued. She improved despite concomitant intravascular coagulation. Multiple cultures from all sites did not identify any source of sepsis.

We suspected azathioprine hypersensitivity owing to:
- The timing of the patient’s illness in relation to the initiation of azathioprine
- The presence of recognised features of hypersensitivity—fever, chills, diarrhoea, hypotension, and hepatic dysfunction
- The effect of rechallenge. Three weeks after the presenting episode, one dose of azathioprine 25 mg was given for steroid-sparing effect (the initial illness was attributed to disease flare up); the patient had a more severe and rapid hypersensitivity response requiring treatment with intravenous corticosteroids and haemofiltration in intensive care.

She improved after treatment with high dose corticosteroids. No cultures ever isolated an infective source.

This case shows the importance of recognising azathioprine hypersensitivity. Approximately 50 cases have been reported in patients with immune mediated diseases such as inflammatory bowel disease, multiple sclerosis, and immune thrombocytopenias, where the initial illness is often ascribed to sepsis or reactivation of underlying disease. Most reactions occur in the first four weeks of drug initiation. Hypersensitivity should always be included in the differential of fever, hypotension, and renal failure. The case was reported to the Committee on Safety of Medicines (United Kingdom).

The mechanism of the reaction is unclear. Azathioprine is composed of a nitroimidazole attached to 6-mercaptopurine. It is proposed that the imidazole component causes hypersensitivity, while the 6-mercaptopurine may cause haematological side effects. However, there are conflicting reports about the component of the drug to which the hypersensitivity reaction can be attributed. Fields reviewed 49 cases, where the reaction occurred equally in men and women, aged 16–76 years, and there was a wide variation in azathioprine doses. All patients who developed shock were also taking corticosteroids.

Support for an allergic reaction is that it occurs in only a small percentage of patients, and the event recurs with drug rechallenge, as occurred inadvertently in our patient. Rechallenge with azathioprine is therefore dangerous and should be done under careful observation. A hapten from the imidazole component may bind to a protein molecule to elicit type 1 hypersensitivity. Reactions mimicking sepsis may result from increased production of mediators such as tumour necrosis factor.

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Figure 1  (A) A view of the patient’s feet three weeks after the initial presentation, showing demarcating digital ischaemia; (B) a close up view showing marked digital peripheral ischaemia.
**Immunosuppressive treatment for vasculitis associated with Lyme borreliosis**

Vasculitis of the central nervous system is a rare complication of Lyme borreliosis. We now report a case of early onset borrelia associated encephalitis followed by systemic vasculitis. Antibiotics failed to improve the clinical course and remission was only reached after extensive immunosuppressive treatment.

A 52 year old man was admitted because of fever, headache, tinnitus, and painful joints. He reported a tick bite on his left arm, which had occurred three weeks earlier and which was followed by a reddish skin eruption. His general practitioner started treatment with doxycycline, but the patient’s condition worsened. The patient had a fever of 39.9°C, further physical examination showed no other abnormalities. Except for an erythrocyte sedimentation rate of 51 mm/1st h and a leucocyte count of 16.1×10⁹/l, routine blood analysis was normal. Cultures (blood, urine, stool) were negative. Enzyme linked immunosorbent assays (ELISAs) showed an increased anti-borrelia-IgM titre of 322.4 EU/ml (normal <30) with normal IgG levels, suggestive of early stage Lyme borreliosis. This was supported by western immunoblotting, with reactivity towards anti-borrelia-IgM.

Intra-venous ceftriaxone (2 g daily) was started. Because of signs of meningoencephalitis the patient was transferred to the intensive care unit (ICU). Analysis of the cerebrospinal fluid (CSF) showed anti-borrelia-IgM antibodies, pleocytosis, and an increased protein level, consistent with neuroborreliosis. An artificially increased IgM level in the CSF owing to the introduction of blood during the spinal tap was ruled out, because few erythrocytes were seen.

Shortly upon arrival at the ICU the patient was intubated and mechanically ventilated because of respiratory insufficiency due to muscle fatigue. Examination now disclosed numerous splinter haemorrhages distributed over the whole body. Ceftriaxone was continued for 10 days and then replaced by doxycycline. After 18 days antibiotic treatment was discontinued because of lack of improvement. Fever persisted and generalised epileptic seizures complicated the course. Cultures remained negative. An ELISA was repeated after four weeks: the anti-borrelia-IgM was then raised to 800 EU/ml; the IgG level was also above normal. The number of splinter haemorrhages increased and a non-oliguric renal insufficiency developed, resembling a glomerulonephritis with microscopic haematuria, granular casts, and proteinuria (0.9 g/24 h). Screening markers of autoimmune diseases (antineutrophil cytoplasmic antibodies, antinuclear antibodies, cryoglobulins) were negative. A skin-fascia-muscle biopsy sample taken from the right leg showed vasculitis of medium sized arteries (fig 1). No spirochaetes were detected in this sample. Treatment with prednisolone (1 mg/kg/day) did not improve the condition of the patient within one week, therefore, cyclophosphamide (2 mg/kg/day) was added. Within two days the patient regained normal neurological functions. Renal function improved within four weeks (serum creatinine decreased from 56.4 to 24.4 mmol/l of urea) and the patient was weaned from the ventilator. Follow up was uneventful.

Vasculitis may develop within weeks after infection and complicate the clinical course of Lyme borreliosis. To our knowledge, this is the first description of a systemic vasculitis including cerebral and renal disease after Borrelia burgdorferi infection in a human being. Histological proof for vasculitis was assessed in a skin-fascia-muscle sample; the absence of spirochaetes therein suggests an autoimmune based pathogenesis. As in this case, laboratory support for acute B burgdorferi infection is an important issue, especially in areas like the Netherlands. Whether elicited directly by the micro-organism or by secondary autoimmune mechanisms, vasculitis occurs in association with disseminated organ failure. Cyclophosphamide, successful in a case of B burgdorferi induced cerebral vasculitis, was effective for this case of systemic vasculitis as well.

In conclusion, persisting vasculitic activity should be suspected whenever antibiotic treatment does not improve the clinical course in Lyme borreliosis. When borrelia associated vasculitis has been histologically established, and does not respond to corticosteroid treatment alone, we suggest the combined use of prednisolone and cyclophosphamide.

**Bilateral transient osteoporosis of the knee in pregnancy**

Transient osteoporosis of pregnancy involving the hips has been reported widely. The knee is much less commonly affected and only isolated cases have been reported. We report the case of a woman in the third trimester of pregnancy with bilateral transient osteoporosis of the knees.

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**Figure 1** Skin-fascia-muscle biopsy sample showing vasculitis of a medium sized artery and some necrosis of the vessel wall.

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**R KOMDEUR**

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**T S VAN DER WERF**

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A 36 year old woman presented with a one month history of pain in the left knee followed a week later by pain in the right. The right knee deteriorated over one to two weeks until she was unable to weight bear. There was no pain at rest. At the time of presentation she was 30 weeks pregnant with her first child conceived through in vitro fertilisation. There was no past history of joint problems, alcohol excess, corticosteroid use, or other complications are recognised accompanying systemic lupus erythematosus. Antibodies against nuclear components are the hallmark of SLE, but a number of antibodies against proteins, glycoproteins, and carbohydrates have also been reported. Dyslipoproteinaemia and accelerated atherosclerosis that commonly lead to coronary artery disease and other complications are recognised sequelae. The role of autoimmunity in the aetiology of atherosclerosis has recently been highlighted. Increased levels of antibodies against oxidised low density lipoprotein, lyso-phosphatidylcholine, and apolipoprotein A1 were found in patients with SLE. As reported earlier, we have shown marked alterations of anticholesterol antibody levels in patients with systemic lupus erythematosus.

Figure 1 Magnetic resonance imaging at presentation. The T1 weighted sagittal image of the right knee shows diffuse low signal in the posterior aspect of the lateral femoral condyle. Note the low signal fluid in the knee joint cavity.
(ACHA) levels in patients with various atherosclerotic vascular disorders. In this study ACHA levels of patients with SLE were compared with those of healthy donors.

Sixty eight patients (64 women, four men), aged 39.4 (10.6) (mean (SD)) years, who fulfilled at least four of the diagnostic criteria established by the American Rheumatism Association for SLE and 60 healthy donors (55 women, five men), aged 42.6 (8.12), were enrolled into the study. The SLEDAI (SLE Disease Activity Index) score was used to measure disease activity. Patients were considered to have active lupus if they scored at least 2 on the modified SLEDAI scale (calculated by omitting anti-dsDNA and complement C3 and C4, data not shown). No correlation differences were found between patients treated with corticosteroids for inactive disease or those with inactive disease and not receiving corticosteroid treatment (p=0.174). The latter group had not received corticosteroids for at least one year before blood samples were obtained. The difference between the ACHA levels of patients who had or had not experienced vascular events was not significant.

The observed increases of ACHA levels may be related to underlying chronic inflammatory disease. A number of conditions such as dyslipoproteinaemia,1 nephrotic syndrome, and changes in cholesterol membrane domains2 might have elicited the increase of ACHA levels. Corticosteroid treatment might also have stimulated ACHA production, though according to our observations this effect was not significant. A preventive role against atherogenic effects might have elicited the increase of ACHA levels, though according to our observations this effect was not significant.

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Intravenous immunoglobulin for treatment of gastrointestinal haemorrhage in dermatomyositis

Polyvisositis (PM) and dermatomyositis (DM) are systemic inflammatory disorders affecting skeletal muscles and other organs, especially the digestive tract.3 Oesophageal motor disturbances are common, occurring in as many as 25–60% of patients with PM/DM.4 Gastrointestinal disease is less recognised in PM/DM, though it may be responsible for life threatening complications—for example, dramatic haemorrhage, perforation, pseudo-obstruction, pneumomatisis cystoides intestinatis, and spontaneous abdominal haematomata.5,6 We recently observed a new case, which is of particular interest. The patient who had DM refractory to steroids and both gastrointesti- nal haemorrhage related to vasculitis and oesophageal impairment due to DM experienced a rapid and complete resolution of all clinical manifestations after intravenous immunoglobulin treatment was started.

An 18 year old man had DM evolving from March 1999. The diagnosis of DM was made by the Bohan and Peter criteria7,8—symmetrical muscle weakness. Muscle power was gauged for eight proximal muscles (neck flexors, trapezius, deltoid, biceps, psoas, maximus and medius gluteus, and quadriceps) by a modification of the British Medical Research Council Grading scale. The 12 patients were evaluated in a theoretical maximum score of 88 points. Muscle power of the patient was 73 points; (b) increased serum muscle enzymes—that is, creatine kinase (CK) 170 U/l (normal 5–11), and aldolase 7.2 U/l (normal 0.5–3.1); (c) myopathic changes on electromyog- raphy; (d) muscle damage on histological examination; and (e) characteristic dermatolo- gical manifestations—that is, heliotrope rash, periangual erythema, and poikiloderma.

Antibodies to TPO were positive (titer 1:320) and autoantibody screen was negative for anti- nuclear antibodies (ANA) with a value of 1:400. Investigations, including pulmonary function tests, computed tomography scan of systemic lupus erythematosus. J Rheumatol 1999;26:2137–43.


Figure 1 Individual anticholesterol antibody (ACHA) levels (mean (SD)) of patients with systemic lupus erythematosus (SLE) (69 (49) AU/ml) and of healthy donors (38 (34) AU/ml). Horizontal lines show median values. (r=0.22, p=0.066). No correlation was found between the ACHA levels and other parameters (such as anti-dsDNA, CH50, C3, and C4, data not shown). No significant differ- ences were found between patients treated with corticosteroids for inactive disease or those with inactive disease and not receiving corticosteroid treatment (p=0.174). The latter group had not received corticosteroids for at least one year before blood samples were obtained. The difference between the ACHA levels of patients who had or had not experi-enced vascular events was not significant.

The inter- and in-variant cross of these methods were 8.7% and 9.5%, respectively. Differences between the parameters mea- sured in controls and patients with SLE, between patients with active and inactive SLE, and those between patients with and without previous vascular events were calculated with the Mann-Whitney-test. The χ2 test was used to estimate the discriminative power of ACHA between patients with SLE and healthy donors. The correlation of individual parameters with each other and with the SLEDAI score was calculated using Spearman’s rank correlation test.

Twelve samples (18%) were classified as having been obtained from patients with active SLE and 56/68 (82%) from patients with inactive disease. Three of the 12 “active” samples were from patients with SLE active in more than one organ system and nine were from patients with disease activity in one organ system only (musculoskeletal (four), central nervous system (two), renal (two), and cutaneous (one)).

The difference between ACHA levels measured in the control group and in patients with SLE was significant (p<0.001) (fig 1). High ACHA levels in the upper quartile occurred in 29/68 (43%) patients with SLE and 13/60 (22%) controls (p=0.012). ACHA levels (mean (SD)) of patients with active (97 (81) AU/ml) or inactive (64 (38) AU/ml) SLE did not differ significantly (p=0.21) and did not correlate with the SLEDAI score

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the lungs, echocardiography, and abdominal ultrasound were normal. Treatment with prednisone was started at a dose of 1 mg/kg daily. As both the clinical and biochemical status continued to deteriorate gradually, the steroid regimen was increased to a dose of 1.5 mg/kg with 1 mg/kg slow taper.

In July 1999 the patient presented with a two week history of dysphagia and melaena evolving from one day. On admission, his general condition was poor and abdominal palpation was tender. Physical examination also showed cutaneous manifestations of DM and muscle weakness affecting both arms and legs. Muscle power of the patient was 65 points. Laboratory findings were as follows: erythrocyte sedimentation rate 50 mm/1st h, C reactive protein 30 mg/l, haemoglobin 6.6 g/l, platelet count 490 x 10^9/l, white blood cell count 10 x 10^9/l, platelet count 490 x 10^9/l, CK 3000 U/l, and aldolase 13.5 U/l. Findings of renal and liver tests, total protein, and albumin levels were normal. Autoantibody screening was positive for ANA >1:1000 with a speckled pattern; other tests, particularly for antinuclear factors, rheumatoid factor, antithyroid antibodies, anti-cardiolipin and antiphospholipid antibodies, lupus-like anticoagulant, antineutrophil cytoplasmic antibodies, and cryoglobulin, were negative. Oesophageal manometry showed decreased peristalsis in the upper third of the oesophageal body and normal pressure in both upper and lower oesophageal sphincters. Gastroscopy demonstrated multiple small ulcerations affecting the stomach and the duodenum, with histology showing vasculitis of the small sized vessels.

A diagnosis of gastrointestinal haemorrhage related to vasculitis and oesophageal impairment due to DM was made. The patient was given intravenous immunoglobulin at a dose of 1 g/kg for two consecutive days monthly for six months. Prednisone was simultaneously decreased gradually to 5 mg every 15 days. The patient had no gastrointestinal haemorrhage recurrence, swallowing disorders and muscle strength improved rapidly, and the dermatological signs cleared.

In November 1999 methotrexate treatment was started at a dose of 30 mg weekly. At one year follow up, the patient remains free of digestive, cutaneous, and muscle symptoms with methotrexate at a dose of 30 mg weekly and 12 mg prednisone daily.

In addition, oesophageal motor abnormalities predominated in patients with PM/DM and have been extensively described, involvement of the gastrointestinal tract is considered to be less common.1 2 In a review of 96 patients with DM, Downey et al found that only four patients had gastrointestinal manifestations.3 Our findings confirm that gastrointestinal impairment is a major cause of morbidity in PM/DM, as our patient presented with life threatening gastrointestinal haemorrhage. A diagnosis of gastrointestinal vasculitis related to DM could reasonably be made for our patient because the onset of DM clinical deterioration and gastrointestinal haemorrhage is consistent and there is no search for other causes of vasculitis (notably systemic vasculitides or other connective tissue disorders) proved negative.

Our report further highlights the importance of recognising gastrointestinal complications at an early stage in PM/DM, resulting in accurate diagnosis and management, and therefore decreasing both morbidity and mortality. The pathological mechanism of gastrointestinal involvement are still not clearly understood in PM/DM, though it may be related to vasculitis of small sized vessels, leading to ischaemia, haemorrhage, and perforation of the gastrointestinal wall.4 5 Moreover, the present case is original, as our patient with DM and life threatening digestive impairment received intravenous immunoglobulin treatment, which prevented gastrointestinal haemorrhage recurring and produced dramatic and rapid remission of swallowing disorders. Other authors have also mentioned a favourable outcome with intravenous immunoglobulin treatment in patients with systemic vasculitis—for example, Churg-Strauss vasculitis, microscopic polyangiitis5–7 and lupus erythematosus.8 9 In this instance, a limitation was the concomitant continuation of steroids during the entire period of intravenous immunoglobulin treatment. However, the improvement of all gastrointestinal symptoms may reasonably be related to intravenous immunoglobulin's immunomodulatory actions in our patient with DM because the gastrointestinal manifestations deteriorated persistently despite high doses of prednisone as a single treatment. The beneficial effect of the accompanying methotrexate treatment could also be excluded, as this later drug was started at the five month follow up of the patient. Finally, our findings indicate that intravenous immunoglobulin should be considered the best treatment in both gastrointestinal haemorrhage related to vasculitis and oesophageal dysfunction due to steroid re-fractory DM, such a treatment offering the advantages of efficacy and good tolerance. However, no definite conclusion can be drawn and further controlled trials with a large number of patients with PM/DM are required to establish optimal doses and effective management.

Sjögren’s syndrome: an unusual cause of Bell’s palsy

The most common form of facial paralysis is idiopathic—that is, Bell’s palsy. Sjögren’s syndrome (SS), a chronic inflammatory disorder characterised by lymphocytic infiltration of exocrine glands resulting in the so called “sicca complex”, is a rare secondary cause of this self limiting illness. Primary SS includes mostly peripheral, and to a lesser extent central, autonomic neuropathy and central nervous system involvement.1 A patient with unilateral facial palsy, autoimmune hypothyroidism, and Sjögren syndrome is presented.

A 41 year old woman developed right sided facial numbness, described as “dentist anaesthesia for tooth extraction”. One day later she had a reduced sense of taste and right facial weakness. General physical examination was not remarkable. Neurological examination showed anisocoria, peripheral right sided facial paresis, reduced sense of taste on the right half of the tongue, and dysaesthesia in the right trigeminal nerve.

Although the erythrocyte sedimentation rate (ESR) was 30 mm/1st h, routine laboratory investigations were normal, including IgG, IgG index, and oligoclonal bands on electrophoresis, was not normal. Screening tests for herpetic simplex and varicella virus, syphilis, and borrelia in the serum and in the liquor were negative. Magnetic resonance imaging (MRI) of the brain showed no abnormalities. Nerve conduction studies showed peripheral facial paresis. She recovered spontaneously from her symptoms within two months, during follow up the raised ESR persisted.

Review of her medical history uncovered complaints of burning eyes and dry mouth, slight weight gain, and cold intolerance. There was a history of anemia, with the red cell distribution width (RDW) being 18%, as anemia was the most prominent laboratory finding. She denied using any drugs previously. A strongly positive anti-extraneurax antigen (ENA) and SSA antibodies test was shown for further investigation, with negative tests for antinuclear factor/anti-nDNA antibodies and rheumatoid factor and RNP/SS-B/Sm antibodies. Rose-Bengal staining showed corneal punctate lesions (van Bijsterfeld score 6). Lower labial biopsy showed histopathological findings matching the diagnosis of SS with a

focus score of one lymphocyte focus for 4 mm² salivary gland tissue. Additionally, thyroid function tests showed a raised thyroid stimulating hormone (11 mU/L), low free thyroxine (13.0 pmol/L) with positive antithyroid microsomal antibodies and negative antithyroglobulin antibodies.

The clinical, serological, and histopathological manifestations fulfilled the European study group criteria for the diagnosis of SS. The patient was treated with artificial tears and thymus supplements that returned her thyroid function tests to normal.

Prevalence of neuropathy in patients with SS ranges from 10 to 50%. Polynuropathy can be the first clinical manifestation of SS and may even precede sicca symptoms in 40% of patients. However, less frequently, cranial neuropathy can occur with a predisposition to involvement of the trigeminal nerve. The vasculitic damage to vaso nervous pathways documented by pathological studies is associated with a higher incidence of serum ANCA. The correlation of specific ANCA with chronic idiopathic axonal neuropathy has been described previously. 

This case illustrates how facial palsy disclosed the primary SS as an underlying systemic disorder. To our knowledge the combination Bell’s palsy as presenting feature in a patient with SS, and hypothyroidism secondarily to ATTD has not been reported hitherto.

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associated diseases in southern Chinese among whom anti-MPO predominates.

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A case of cholesterol embolism with ANCA treated with corticosteroid and cyclophosphamide

We report a case of a patient with cholesterol embolism who showed positive for both myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) and proteinase 3 antineutrophil cytoplasmic antibody (PR3-ANCA) and who was treated with prednisolone (PSL) and cyclophosphamide.

A 50 year old man underwent cardiac catheterisation for back pain. The examination disclosed 90% stenosis of the right coronary artery and a saccular aneurysm in the thoracic aorta. The patient underwent percutaneous transluminal coronary angioplasty and the aneurysm was wrapped with an artificial blood vessel. Postoperatively, the patient had a fever, pleural effusion, abdominal pain, and increased white blood cell (WBC) count. C reactive protein (CRP), and serum creatinine levels were negative. PSL 15 mg/day was started. However, acute progression of renal failure required haemodialysis.

The patient was transferred to our hospital. Physical examination showed a temperature of 38.0°C and blood pressure of 178/98 mmHg. Cyanosis was noted in both heels and all toes with necrosis and ulcers at the tips of the fifth toes. He had an increased erythrocyte sedimentation rate (ESR) of 82 mm/1st h. Anaemia was noted with a red blood cell count of 2500x10³/µl, while the patient's WBC count was high at 12x10³/µl. His platelet count (304x10³/µl) was within the normal range. Biochemistry showed high levels of blood urea nitrogen (10.0 mmol/l of urea), creatinine (710 µmol/l), and CRP (11.3 mg/l). Complements components were within normal ranges. PR3-ANCA and MPO-ANCA were high at 82E and 29E, respectively.

After admission to hospital, circulatory disturbance in his toes worsened. A diagnosis of ANCA associated vasculitis was made based on systemic inflammatory findings and high levels of WBC, CRP, PR3-ANCA, and MPO-ANCA. High dose steroid treatment was started. Biopsies of the right heel skin and thigh quadriceps showed cholesterol embolism (fig 1). However, PSL treatment was continued together with three courses of cyclophosphamide pulse treatment because of persistent fever and high ANCA values. The treatment reduced the fever and toe necrosis, and the ulcers improved. ANCA gradually decreased to normal. The PSL dosage was reduced to 15 mg/day and the patient was discharged.

Cholesterol embolism predominantly affects elderly men with a history of hypertension, atherosclerotic vascular diseases, and renal insufficiency at the time of diagnosis. At least 31% of patients had a preceding history of anticoagulant use or the antecedent performance of a vascular procedure affecting the arterial circulation.1 The presence of these cholesterol embolisms within the vascular lumen triggers a characteristic localised inflammatory and endothelial vascular reaction. The inflammatory changes resulting from cholesterol embolism may be responsible for many of the systemic manifestations such as fever, weight loss, myalgias, leukocytosis, eosinophilia, and a raised ESR. Thus cholesterol embolism is referred to as both vasculitis look-alikes1 and pseudovasculitic syndrome.2 The prognosis is poor, particularly in the presence of acute renal failure.3 Three ANCA positive cases4 of cholesterol embolism have been described. Peat and Mathieson reported an ANCA positive patient with dyspnoea and haemoptysis after acute deterioration of renal function.5 Cyclophosphamide and PSL improved the symptoms, but cyclophosphamide was discontinued and the PSL dose was reduced because renal and skin biopsies showed cholesterol embolisms. Subsequently, the patient died of intractable cardiac failure.

Kaplan-Pavlovic et al reported two cases of renal failure with positive MPO-ANCA.6 The details are unknown for one patient. The other patient was treated with corticosteroid alone. This patient required haemodialysis and amputation of the toes. Although their treatment did not result in the improvement of vasculitis, the combination of PSL and cyclophosphamide was effective in our patient with ANCA.

This result suggests that active treatment with corticosteroid and cyclophosphamide should be considered in ANCA positive cases of cholesterol embolism.

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HLA-DRB1*0301 and DQA1*0501 in RA

Auranofin is an oral gold preparation used in the treatment of rheumatoid arthritis (RA). During treatment, proteinuria has been reported in approximately 3% of patients. In a few cases in which renal biopsies were performed, a membranous nephropathy was shown to have developed. Several anti-rheumatic agents have been reported to induce renal manifestations or drug induced lupus reactions, or both, in patients with RA. In these subjects a genetic predisposition for HLA has been previously suggested.

To determine whether similar genetic factors might be operative in auranofin induced nephropathy, we analysed the HLA-DRB1*, DQA1*, and DQB1 alleles using a polymerase chain reaction. Furthermore, we investigated if the renal side effects were associated with serological findings in accordance with systemic lupus erythematosus (SLE), thus indicating the development of a drug induced lupus reaction.

Six patients (three female, three male) who developed biopsy proven membranous nephropathy or significant proteinuria (>0.5 g/day) during treatment with auranofin are reported. All patients met the American College of Rheumatology criteria for RA. The median age before onset of auranofin treatment was 72 (52–83) years, 4/6 patients were rheumatoid factor positive and 2/5 patients were antinuclear antibody (ANA) positive. The median duration of auranofin treatment before the onset of proteinuria was 5 (4–10) months.

During auranofin treatment, two patients developed an increased ANA titre (1/200 and 1/1600) but no antibodies against anti-dsDNA, SSA/SSB, Sm, or RNP were detected. None of the patients developed an increased serum creatinine level. After withdrawal of auranofin, proteinuria decreased significantly or disappeared in all cases.

Table 1 presents the HLA alleles.

A high frequency of the alleles associated with SLE—namely, DRB1*0301 (DR3), DQA1*0501, and DQB1*0201, was recorded in the patients developing membranous nephropathy or proteinuria during auranofin treatment. Of these, DRB1*0301 and DQA1*0501 occurred in 4/6 of the patients, and 5/6 patients carried at least one of these alleles.

The importance of DR3 or DQA1*0501 in drug induced renal manifestations has previously been suggested in patients with penicillamine and sodium aurothiomalate induced renal side effects. Also, in accordance with these findings, the DQA1*0501 and DRB1*0301 alleles have been recorded in a high frequency in patients developing sulfasalazine induced nephritis.

In two cases the development of membranous nephropathy was accompanied by a simultaneous increase in the ANA titre, thus indicating development of a drug induced SLE reaction. However, both patients had previously presented some sign of an autoimmune reactivity pattern, which may confer a risk factor in the treatment with certain anti-rheumatic drugs in RA.

Simultaneous treatment with sulfasalazine had been given in two cases, but as the sulfasalazine treatment period was either limited, or lacked any time relation with the onset of proteinuria, it seems unlikely that the patients developed a drug reaction against sulfasalazine. Further arguments rejecting the possibility of a sulfasalazine induced drug reaction are the lack of anti-dsDNA antibodies and the rapid onset of proteinuria among the patients, thus contrasting with the findings reported in sulfasalazine induced SLE.

The mechanism for induction of membranous nephropathy during auranofin treatment is unknown. Interestingly, it has been suggested that gold can bind to and alter major histocompatibility complex-peptide complexes, thus giving a possible explanation of both beneficial effects as well as side effects during treatment. Another possibility is that auranofin may alter the cytokine pattern towards an SLE-like phenotype and thus facilitate the development of SLE associated manifestations in genetically susceptible subjects. In accordance with this hypothesis, auranofin or other gold preparations have been reported to inhibit the production of interleukin 1 (IL1), tumour necrosis factor, and IL2. The effects on IL10, a cytokine reported to be increased in both patients with idiopathic SLE and their healthy relatives as well as in patients developing sulfasalazine induced SLE-like reactions, is unknown, however.

In conclusion, the data suggest that SLE related HLA alleles, with special focus on DRB1*0301 and DQA1*0501, may predispose to development of renal side effects or drug induced lupus reactions during treatment with auranofin, as also previously recorded during treatment with other anti-rheumatic agents. Development of drug induced SLE, here reported for the first time, may occur during auranofin treatment.

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Table 1 HLA DRB1*, DQA1*, and DQB1* alleles in patients with development of renal manifestations during auranofin treatment

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*No renal biopsy was performed in these patients.