LETTERS TO THE EDITOR

Brown's syndrome: an important cause of diplopia in systemic lupus erythematosus

Brown's syndrome is caused by a mechanical limitation of the superior oblique tendon. This simulates a palsy of the inferior oblique muscle with limitation of elevation in adduction. The syndrome can be congenital or acquired. Acquired Brown's syndrome has been described in collagen vascular diseases including rheumatoid arthritis and Still's disease.^{1,2}

Two case reports have described Brown's syndrome in systemic lupus erythematosus (SLE) in adults,^{3,4} but no cases of Brown's syndrome in a juvenile with SLE have been reported to date.

A 14 year old girl was referred to the ophthalmic department with a two day history of diplopia and arthralgia of her hands. She had a three year history of SLE that had been complicated by rashes, arthritis, cerebral vasculitis (two years previously), and was recently under investigation for haematuria. She had been receiving prednisolone in variable doses since the diagnosis was made.

On general examination, the patient had a butterfly rash, cushingoid features, and mild swelling of the small joints of her hands. Ocular examination revealed visual acuities of 6/6 in both eyes. Her eye movements showed restricted elevation in adduction of the left eye. Pupillary responses and other ocular examination were normal. There was tenderness over the left trochlear, but no clicking sound or sensation noted on eye movement. A Hess chart revealed limited elevation in adduction, with no superior oblique overaction of the left eye, consistent with a left Brown's syndrome (figure). The patient declined a forced duction test.

Laboratory studies were consistent with active SLE: leucocyte count $2.8 \times 10^9/l$ (neutro-

phils $2.0 \times 10^9/l$, lymphocytes $0.7 \times 10^9/l$); antinuclear factor was increased to 1600 and DNA antibodies to 1650 IU/ml (normal range up to 60 IU/ml). Serum complement component C3 was 0.64 (normal range 0.8-1.9 g/l) and C4 was <0.08 (normal range 0.12-0.4 g/l).

A diagnosis of Brown's syndrome secondary to SLE was made. The patient's steroids were increased from 5 mg of prednisolone on alternate days to 30 mg per day. Her symptoms improved in one week and completely resolved by two weeks, confirmed by normal Hess test.

Six weeks later, renal investigations showed a plasma creatinine of 70 $\mu\text{mol/l}$, plasma albumin 43 g/l and a normal protein/creatinine index. Renal biopsy revealed mild lupus nephritis (World Health Organisation type 2A). During this hospital stay she had a further episode of vertical diplopia. Computed tomography (CT) and magnetic resonance imaging scans of her head, for presumed intracerebral cause, revealed no local or intracranial pathology. With the combination of diplopia and increased markers for SLE activity, intracerebral involvement was assumed and a course of cyclophosphamide subsequently given on an outpatient basis. Although no ophthalmic assessment was made, a recurrence of her Brown's syndrome was a possibility, and this diagnosis may have prevented the need for cyclophosphamide.

The causes of Brown's syndrome can be divided into two main categories—inflammation and trauma—both involving the muscle, tendon, trochlear, or surrounding tissues of the superior oblique muscle.⁵

Two descriptions of Brown's syndrome associated with SLE have been of a 27 year old woman and a 30 year old man,^{3,4} the former successfully treated with a combination of indomethacin and prednisolone orally, the latter with ibuprofen alone. In our patient, inflammatory markers indicated active SLE and her diplopia was resolved by increasing the dose of her oral steroid.

Diplopia in patients with SLE has usually been attributed to nervous system disease caused by a microvasculitis. The exact cause for Brown's syndrome in SLE is unknown, but is thought to be a tenosynovitis of the superior oblique tendon.

Clinically, patients with Brown's syndrome present with vertical diplopia that is worse on

adducting and elevating the affected eye, often with associated pain and tenderness in the trochlear region. Examination, Hess chart, and forced traction test confirm restricted elevation in adduction. An orbital CT scan may reveal local pathology, but this is not always the case.

Treatment of inflammatory Brown's syndrome is dependent on the cause. In addition to oral steroids and non-steroidal anti-inflammatory drugs,^{3,4} local steroid injections have been used successfully.⁵ In those patients who fail to respond, superior oblique tenotomy combined with inferior oblique recession has been advocated.⁶

This case report illustrates the importance of involving the ophthalmologist in cases of SLE with diplopia. The true incidence of Brown's syndrome in SLE is probably much greater than the few reported cases would suggest. Ophthalmic assessment would help in distinguishing between nervous system disease and this local mechanical problem found in these patients.

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Mechanism of haematuria in lupus nephritis

While the renal manifestations of systemic lupus erythematosus (SLE) vary with the severity of the renal lesion, proteinuria is present in the vast majority of cases. Haematuria, which is less common, is usually microscopic, but may be macroscopic in an occasional patient.¹ Haematuria seems to result from the passage of red blood cells through anatomical gaps in the glomerular basement membrane (GBM). While such gaps have been described in patients with various forms of glomerulonephritis, including those with lupus nephritis associated with haematuria,² the passage of red blood cells (RBCs) through these gaps has been demonstrated only in patients with focal proliferative glomerulonephritis,³ mild proliferative glomerulonephritis,⁴ and membranous nephropathy.⁵ Passage of RBCs has also been demonstrated in our model of experimental glomerulonephritis.^{6,7} We now report a patient with SLE and lupus nephritis in

Hess chart showing limited elevation in adduction, with no superior oblique overaction, of the left eye.

whom a renal biopsy specimen showed the escape of RBC through a gap in the GBM.

This 23 year old Japanese woman was admitted to our hospital for the further evaluation of the nephrotic syndrome associated with SLE. When the diagnosis was first made eight years earlier, she had exhibited a high fever, typical butterfly rash, and pain in both knees. Laboratory tests at that time revealed leucopenia, positivity for serum antinuclear antibody and DNA antibody, and a low level of complement. She received treatment with prednisolone under the supervision of a local physician. One month before the present admission, she felt generally fatigued and developed oedema of the face, hands, and legs. Physical examination on admission revealed a pigmented butterfly rash on the face and leg oedema. Her blood pressure was 106/68 mm Hg. Her heart and the lungs were normal. Urine analysis showed proteinuria of 3.7 g/day, microscopic haematuria (10 RBCs/high power field (HPF)) with dysmorphic erythrocytes, leucocuria (15 leucocytes/HPF), and granular casts. Laboratory study revealed a slight deterioration of renal function (creatinine clearance 64 ml/min, blood urea nitrogen

240 mg/l and creatinine 6.1 mg/l). Serum total protein was 41.2 g/l, albumin 25 g/l and total cholesterol 3430 mg/l. The RBC count was $380 \times 10^4/\text{mm}^3$, leucocyte count $7400/\text{mm}^3$, and platelet count $18 \times 10^4/\text{mm}^3$. Tests for LE cells and for antinuclear factor were both positive. The serum DNA antibody titre was 30 U/ml (normal value (NV) less than 7 U/ml), and serum complement was decreased: haemolytic complement (CH_{50}) 16.6 U/ml (NV 30–40 CH_{50} U/ml); C3 262 mg/l (NV 450–870 mg/l); C4 119 mg/l (NV 120–370 mg/l).

Examination of a percutaneous renal biopsy specimen by light microscopy revealed 10 glomeruli, one of which showed global sclerosis. One other glomerulus showed crescent formation and the remaining glomeruli showed evidence of a mild proliferative lesion with focal wire loop and hyaline thrombi. Immunofluorescent microscopy revealed a fine granular pattern along the glomerular capillary wall with a slight mesangial staining pattern for antihuman IgG, C3, and C1q.

Electron microscopic study revealed an increased number of mesangial cells and an

infiltration of leucocytes to the glomeruli. Electron dense deposits were observed mainly in the subepithelial region, with less localisation in the mesangium and subendothelium. Some electron dense deposits occupied the entire layer of the GBM. Striking changes in the GBM included a generalised thickening, attenuation, irregularity, wrinkling, notching, and rupturing. Numerous red blood cells with an irregular surface were observed in the urinary space (figure, A). The RBCs in the capillary lumen were smooth. Escape of RBCs was observed from the capillary lumen into the urinary space close to the site of mesangial interposition (figure, B). Epithelial cells showed vacuolation and fusion of the foot processes. Microscopic findings were compatible with a diagnosis of diffuse membranous glomerulonephritis associated with lesions of diffuse glomerulonephritis. The World Health Organisation morphological classification was lupus nephritis IV-d.

The escape of red blood cells through a gap in the GBM was demonstrated in this patient with lupus nephritis. The cause of this rupture is not completely understood. Several factors seem to be involved in damaging the GBM and in leading to its perforation. Patients with the immune complex type of glomerulonephritis exhibit rupture of the GBM in areas in which the thickness of the basement membrane is infiltrated by electron dense deposits.^{2,4} Such deposits may replace or greatly interfere with the structure of the GBM and thus create points of weakness to even simple mechanical factors.²

Leucocyte protease is important in the mechanical disruption of the GBM. The migration of polymorphonuclear leucocytes^{2,7} and of monocytes⁸ into Bowman's space has been reported. Exudation of leucocytes in the glomerulus and in the urine are characteristic of lupus nephritis. The urinary sediment that contains erythrocytes, leucocytes and various casts is termed 'telescoped sediment'.⁹ Thus the leucocytes in the urine may also originate from glomerular capillary.

One characteristic of glomerular bleeding is the excretion of dysmorphic RBCs in the urine. The RBCs that originate in the glomerulus are dysmorphic, whereas those that originate in other parts of the urinary tract are uniformly isomorphic.¹⁰ The altered morphology of the RBCs that originate in the glomerulus may reflect the mechanism of their entry from the capillary lumen into the urinary space, as described by Lin *et al.*⁵ Those authors showed that, in a case of membranous nephropathy with structural gaps in the GBM, the deformability of the RBCs allowed them to be pushed through the gaps into the urinary space. They suggested that the combined forces of the pulsatile glomerular capillary hydraulic pressure and the elasticity of the GBM, while pushing the red cells through these gaps, also produced shearing stresses to the red cell surface, thus causing deformation.

This is the first report demonstrating the morphological basis of haematuria in lupus nephritis.

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A: Low magnification (original $\times 1200$) of electron micrograph showing many red blood cells in the urinary space (arrows). **B:** Partial enlargement of A demonstrating the escape of a red blood cell through a gap (arrows) in the GBM. Note the $1 \mu\text{m}$ long process of the red blood cell that is crossing the basement membrane. Note smooth surface of RBCs in the capillary lumen (CL), in contrast to the irregular surface of RBCs in the urinary space (US). Subepithelial (arrowheads) and mesangial (*) deposits are visible. Ep = epithelial cell; Ed = endothelial cell; MC = mesangial cell. Original magnification $\times 4000$.

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Successful application of high dose intravenous immunoglobulins in Sjögren's syndrome associated arthritis

High dose intravenous immunoglobulins (IVIg) have become an important treatment in a number of autoimmune disorders.¹ Both controlled² and uncontrolled^{3,4} studies have demonstrated beneficial effects of IVIg in rheumatic diseases such as dermatomyositis,² rheumatoid arthritis,³ and systemic lupus erythematosus.⁴ We report our experience with IVIg in a patient with Sjögren's syndrome.

A 39 year old man presented for the first time in 1992 with a three year history of painful swelling of both parotid glands without signs of infection. A keratoconjunctivitis sicca which had been confirmed by Schirmer's test required the use of tear substitutes. In addition, the patient had developed an incapacitating, non-erosive arthritis involving both wrists, the metacarpophalangeal and proximal interphalangeal (PIP) joints, the knees, and the ankles. Serological evaluations revealed high titres of antinuclear antibodies (ANA), anti-Ro(SS-A) and anti-La(SS-B) antibodies, and increased titres of rheumatoid factor. Serum IgG was increased to 30.4 g/l without IgG subclass imbalance.⁵ The patient fulfilled four of the six 1993 criteria for the diagnosis of Sjögren's syndrome.⁶ Treatment with NSAID was initiated because of persisting arthritis, but without success. Prednisolone was effective

in doses up to 30 mg per day, but had to be withdrawn because of signs of iatrogenic Cushing's syndrome, including hypertension and impotence. Treatment with methotrexate was refused by the patient because of the risk of impaired fertility.

We therefore decided to institute IVIg treatment. The patient received 30 g of a sulphated IVIg preparation (Venimmun^R, Behringwerke AG, Marburg, Germany) on each of days 1 to 4 and 21 to 24. Except for one period of headaches, the IVIg were well tolerated and led to a remarkable improvement in the arthritis as manifested by a reduction in the cumulative PIP joint circumference from 562 mm before treatment to 550 mm at day 30, and a simultaneous increase in grip strength from 80/180 mm Hg (left/right) to 280/300 mm Hg. In addition, a distinct resolution of the patient's parotid gland swelling was noted. Serologically, IVIg treatment resulted in an increase in serum IgG to 56.0 g/l at day 5 and to 41.1 g/l at day 30. While titres of ANA, anti-Ro(SS-A), and anti-La(SS-B) antibodies were not affected, the erythrocyte sedimentation rate decreased from 32 mm/1st h to 5 mm/1st h within 50 days, accompanied by a parallel decrease in C reactive protein from 22 mg/l to 8.5 mg/l. The beneficial effects lasted for a total of three months. During month 4, moderate joint pain recurred, but it was controlled adequately by NSAID for the ensuing two months. However, at the end of month 6 a severe relapse of arthritis occurred. IVIg treatment was reinstituted, followed again by a distinct relief of joint swelling and pain.

Our observations suggest a beneficial effect of IVIg in a patient with Sjögren's syndrome associated arthritis, which is one of the most common extraglandular disease manifestations of this symptom complex.⁷ Although spontaneous remission cannot be excluded definitively, this seems to be unlikely because the clinical improvement closely followed IVIg administration and was reproducible in a flare of the disease. To our knowledge, this is the first description of the application of high dose IVIg in Sjögren's syndrome. As many patients with this condition present with increased IgG levels, they are considered at risk of developing symptoms of hyperviscosity,⁸ however, despite high IgG levels before treatment, no major side effects occurred in our patient. Although our observation in a single patient requires confirmation in others, it does suggest an additional therapeutic option for selected Sjögren's syndrome patients with extraglandular manifestations in whom conventional treatment fails or is contraindicated.

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Asymmetrical nodular osteoarthritis in a patient with a hemiparesis

A 69 year old woman presented to our department complaining of pain and swelling affecting the fingers of the right hand and which had developed over the preceding 10-15 years. There were no symptoms arising from the left hand, which was affected by a hemiparesis, a consequence of the surgical resection of a cerebral tumour at the age of 12. On examination, the patient had a left hemiparesis with a mild pyramidal weakness and loss of sensation to light touch. She had Heberden's and Bouchard's nodes affecting all the interphalangeal joints of the right hand, but none on the left (fig 1).

The patient had worked full time as a clerk for 41 years, during which time she was predominantly right handed, but used her left hand for light manual tasks. She gave a very clear description of a similar arthritis affecting her mother who, she recalled, had marked symmetrical deformity of her proximal (PIP) and distal interphalangeal (DIP) joints.

Radiographs confirmed the diagnosis of nodular generalised osteoarthritis (OA) with osteophytic lipping, sclerosis, and joint space narrowing of the affected joints (fig 2). Serological tests were normal and erythrocyte sedimentation rate was within normal limits for her age.

Osteoarthritis is the commonest joint disorder in Western populations, and the hand the most frequent site of involvement.¹ Nodular generalised OA affects the joints of the hand in a symmetrical manner, the most frequent joint groups involved being the DIP and thumb base. In a recent population study,² the tendency for symmetry was pronounced for both the DIP and PIP joints, and was greater than that for row or ray clustering. For OA affecting the DIP joint, the odds ratio for contralateral involvement of the same joint was 38.8 (95% confidence interval (CI) 14.5-103); for any other DIP in the same hand it was 11.5 (95% CI 7.8-17.0). It is highly likely, therefore, that joint involvement of nodular generalised OA of the hand will be found to be symmetrical.

Asymmetrical OA of the hands has been described occasionally in similar circumstances. In 1947, Stecher and Karnosch described a woman with a median nerve injury of the hand who later developed Heberden's nodes in all her fingers except those supplied by the injured nerve.³ Stecher also described it in a hand paralysed by poliomyelitis,⁴ and in 1935 Coste and Forrester reported a case that occurred after a cerebral accident.⁵