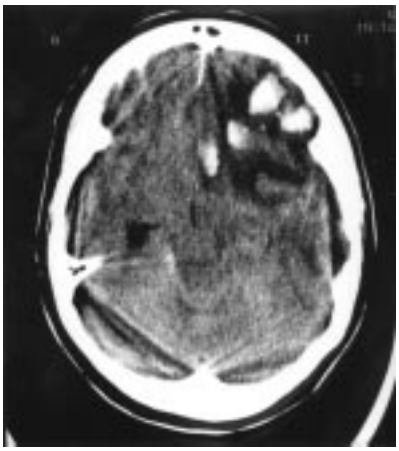

Brain CT after clinical deterioration. There is extensive patchy haemorrhage into the left frontal lobe with marked mass effect.

Macroscopically the left frontal lobe was swollen, with multiple small areas of haemorrhage in the cortex and white matter, and thrombosis of superficial cortical veins. Histological examination disclosed a coexistant pattern of granulomatous and necrotising non-granulomatous vasculitis affecting the small leptomeningeal and intracerebral blood vessels. Occasional leptomeningeal vessels were occluded by thrombus.The granulomatous lesions featured an infiltrate of lymphocytes and histocytes within blood vessel walls. The vascular intima was variably thickened by a fibrocellular proliferation and small numbers of Langhans and foreign body type giant cells were scattered individually within the media of some vessels.The leptomeninges contained a dense infiltrate of mononuclear inflammatory cells. The cerebral tissues were oedematous with extensive extravasation of erythrocytes and diffuse hypoxic neuronal changes but there was no evidence of a discrete area of infarction. Special stains for organisms (zinc, gram, PAS, PAS-D, Giemsa and GMS) were negative. Viral inclusions were not seen.

Haematological investigation disclosed a mild neutrophil leucocytosis, but haemoglobin, platelet count, and erythrocyte sedimentation rate were all in the normal range as were serological investigations including C reactive protein, complement assays, antinuclear antibodies, double and single stranded DNA antibodies, and rheumatoid antibodies.

The patient was treated intensively with a combination of oral cyclophosphamide and intravenous methyl prednisolone for one week followed by oral cyclophosphamide and prednisone. Treatment was complicated by haemorrhagic cystitis (for which oral cyclophosphamide was changed to pulsed intravenous cyclophosphamide), and organic psychosis. At 2 years the patient is clinically stable. Immunotherapy is being gradually reduced. She has a fixed frontal lobe deficit consisting of impulsivity, a loss of control of emotions, reduced verbal fluency, and impaired insight. Serial CT and MRI show only postsurgical change in the left frontal lobe.

The importance of this case is firstly that it draws attention to the protean manifestations of this rare but treatable condition. Other reported presentations include recurrent intracerebral haemorrhage, radiculomyelopathy, cerebral and spinal aneurysms, subarachnoid haemorrhage, seizures, and mass lesions.[1 2 5]

Secondly, this case emphasises the fact that the disease mostly affects small vessels of the leptomeninges. Neurosurgeons are most likely to encounter this disease in the setting of a request by their neurology colleagues for a diagnostic brain biopsy. Moore suggested that the ideal biopsy in these patients is a 1 cm wedge of cortex including leptomeninges and preferably containing a cortical vessel.[1]

Our patient ultimately required urgent decompressive frontal lobectomy. The diagnosis of GANS was not suspected preoperatively and the inclusion of leptomeninges in the surgical specimen was fortuitous. We would advise others undertaking the evacuation of an intracerebral haematoma of uncertain aetiology to obtain a leptomeningeal biopsy at the same time, particularly when there is a background of neurological symptoms.

Other investigations may not be helpful. Brain CT and MRI are abnormal in 30%-65% and 75%-100% of cases respectively and may show a wide variety of lesions. Angiographic abnormalities are present in 50%-90% of cases but are not specific for GANS. The CSF may be normal.[1 2] It is essential to differentiate GANS, from the many secondary causes of cerebral vasculitis such as giant cell arteritis. The presence of markers of systemic, inflammatory, or autoimmune disease should suggest an alternative diagnosis.

Because GANS is rare, our knowledge of its natural history and optimum management is incomplete. Early reported cases of GANS were invariably fatal[5] but immunotherapy has now been shown to improve symptoms and result in sustained remission in some cases. The results with corticosteroids alone have been disappointing and the combination of prednisone with cyclophosphamide is the mainstay of treatment.[1 3 5]

MARTIN HUNN
SIMON ROBINSON
Department of Neurosurgery

LEN WAKEFIELD
Department of Pathology

STUART MOSSMAN
DAVID ABERNETHY
Department of Neurology, Wellington Hospital, Wellington, New Zealand

Correspondence to: Mr Martin Hunn, Neurosurgical Unit, Wellington Hospital, Capital Coast Health Ltd, Private Bag 7902, Wellington South, New Zealand.

1 Moore P. Diagnosis and management of isolated angiitis of the central nervous system. *Neurology* 1989;**39**:167–77.
2 Voller TM, Guaranaccia J, Harrington W, *et al*. Idiopathic granulomatous angiitis of the central nervous system. Diagnostic challenges. *Arch Neurol* 1993;**50**:925–30.
3 Ozawa T, Sasaki O, Sorimachi T, *et al*. Primary angiitis of the central nervous system: report of two cases and review of the literature. *Neurosurgery* 1995;**36**:173–9.
4 Biller J, Loftus CM, Moore SA, *et al*. Isolated central nervous system angiitis first presenting as spontaneous intracranial haemorrhage. *Neurosurgery* 1987;**20**:310–15.
5 Koo EM, Massey EW. Granulomatous angiitis of the central nervous system: protean manifestations and response to treatment. *J Neurol Neurosurg Psychiatry* 1988;**51**:1126–33.

Intravesical atropine suppression of detrusor hyperreflexia in multiple sclerosis

Multiple sclerosis commonly causes urinary frequency, urgency, and urge incontinence resulting from detrusor hyperreflexia. This might be associated with voiding difficulties due to detrusor sphincter dyssynergia. These symptoms can be treated effectively with antimuscarinic drugs (principally oxybutynin) and clean intermittent catheterisation, but the antimuscarinic side effects limit clinical usefulness. Typically these are dry mouth and blurred vision, but include constipation, reflux oesophagitis, and flushing.

Oxybutynin, formulated for intravesical administration, has been reported to be effective for suppressing detrusor hyperreflexia with low incidence of side effects in various neuropathic disorders.[1 2] However, this preparation is not widely available.

Atropine is a cheaper, easily obtainable, antimuscarinic drug. Administered intravesically it has been shown to be effective in increasing bladder capacities without side effects in patients with spinal cord injury.[3] However, the only study was small and uncontrolled. Whereas the pathologies of multiple sclerosis and spinal cord injury are different, the bladder impairments are similar. This study was designed to investigate the efficacy of intravesical atropine in increasing bladder capacities in patients with multiple sclerosis with detrusor hyperreflexia.

The study received ethics committee approval. Written informed consent was obtained from each patient.

Patients with a definite diagnoses of multiple sclerosis and urodynamically demonstrated detrusor hyperreflexia were recruited into the study. Each was taking oral antimuscarinic medication and using clean intermittent catheterisation. A sample size calculation based on previous data[3] identified a target recruitment of 15 patients to achieve a significance level of 0.05 with a power of 0.80 using a crossover study design. Eighteen patients were contacted, of whom 16 consented and 15 completed the study.

Antimuscarinic drugs were stopped 2 days before cystometric testing. Patients attended on two occasions. They were allocated 30 ml of either atropine (6 mg) in normal saline or normal saline only (as placebo). This was done according to random code with both patient and investigator blinded. An independent nurse prepared the solutions.

Standard static saline fill cystometry with a filling rate of 50 ml/min was performed before and 2 hours after intravesical instillation of the test preparations. As this was a first randomised study of a single dose of intravesical drug the outcome measure used was cystometric bladder capacity and not urgency or episodes of urge incontinence. A single prophylactic dose of ciprofloxacin (250 mg) was administered orally on each occasion. At the beginning and end of each cystometric study the patient's heart rate and blood pressure were measured. All patients were questioned about known antimuscarinic side effects. Blood samples were collected for atropine assays 2 hours after instillation of the test solutions.

Urodynamic data were not normally distributed, therefore non-parametric analysis techniques were used. When comparisons between the difference in change in cystometric bladder capacities were made a Wilcoxon sign ranked test was used quoting the 95% Wilcoxon confidence interval.

The study group consisted of 15 patients (six men and nine women) with a median age of 51 years (range 39–73 years). All patients retained their test solutions after each instillation. The results are shown in table 1. After atropine the bladder volumes increased by a

Cystometric bladder capacities (CBC) for atropine and placebo (saline)

	CBC (ml) (95% CI)	*Change in CBC (ml) (Wilcoxon 95% CI)*
Atropine		
Pretreatment	183 (144.5-302.5)	
Post-treatment	350 (195.3-451.3)	93 (45 to 170)
Saline		
Pretreatment	180 (124.6-312.8)	
Post-treatment	159 (143.7-331.8)	−2.5 (−21.5 to 14.5)

median value of 93 ml (95% confidence interval 45.0–170 (p=0.001)). After saline the cystometric bladder capacity did not change significantly.

No significant changes were found in blood pressures or pulse rates. No side effects were reported by any patient. Atropine was not detected in blood samples 2 hours after intravesical instillation (limit of detection 0.05 mg/l).

This early study provides evidence in favour of the efficacy of intravesical atropine in increasing the cystometric bladder capacity in patients with multiple sclerosis. Cystometric bladder capacity was chosen as an outcome measure because it has been shown to be sensitive to the influence of orally administered antimuscarinic drugs used for the treatment of detrusor hyperreflexia in multiple sclerosis.[4] It is therefore likely that urgency and urge incontinence will be improved with the administration of intravesical atropine. However, this will require testing in a randomised controlled therapeutic trial.

The patients did not identify any side effects during the 2 hours after the administration of the atropine. It has been shown that orally administered oxybutynin will induce antimuscarinic side effects in a similar period.[5]

The absence of measurable drug in the blood at the time of the clinical effect is encouraging. The results show promise and if clinical efficacy were demonstrated this approach would be a useful addition to the therapeutic options for urinary incontinence in multiple sclerosis.

The study was funded by the MS trust fund of the Central Middlesex Hospital London. We thank Professor Stephen Senn of the Department of Epidemiology and Public Health at University College London for statistical advice.

CARL DEANEY
Academic Department of Surgery, Imperial College School of Medicine, Charing Cross Hospital, London W6 8RF, UK

SCOTT GLICKMAN
Department of Medical Rehabilitation, Imperial College School of Medicine, Charing Cross Hospital, London W6 8RF, UK

TIMOTHY GLUCK
Medicine for the Elderly, Barnet General Hospital, Wellhouse Lane, Barnet, Herts, EN5 3DJ, UK

JAMES G MALONE-LEE

Correspondence to: Professor James G Malone-Lee, Department of Geriatric Medicine, University College London Medical School, St Pancras Hospital, 4 St Pancras Way, London NW1 0PE, UK.

1 Wesse DL, Roskamp DA, Leach GC, *et al*. Intravesical oxybutynin chloride: experience with 42 patients. *Urology* 1993;**41**:527–30.
2 Greenfield SP, Fera M. The use of intravesical oxybutynin chloride in children with neurogenic bladders. *J Urol* 1991;**146**:532–4.
3 Glickman S, Tsokkos N, Shah PJR. Intravesical atropine suppression of detrusor hypercontractility in the neuropathic bladder. A preliminary study. *Paraplegia* 1995;**33**:36–9.
4 Gajewski J, Awad SA. Oxybutynin versus propantheline in patients with multiple sclerosis and detrusor hyperreflexia. *J Urol* 1986;**135**: 966–8.
5 Collas D, Malone-Lee JG. The pharmacokinetic properties of rectal oxybutynin—a possible alternative to intravesical administration. *Neurourology and Urodynamics* 1997;**16**:346–7.

Prothrombotic mutations and ischaemic stroke at a young age in two sisters

We examined two sisters who had an ischaemic stroke at 32 and 41 years respectively. One had the prothrombin 20210 G to A variant[1] and mild hyperhomocysteinaemia. The other had two prothrombotic mutations: the factor V Leiden mutation[2] and the prothrombin 20210 G to A variant.[1] We argue that these abnormalities may have caused the strokes.

Patient III-36 (pedigree, figure) was admitted at the age of 41 years with a left sided paresis. Her medical history was unremarkable, including the absence of migraine. Neurological examination showed a mild left sided paresis. Blood pressure was normal. She had no livedo reticularis. Brain CT showed a right sided cerebral infarct. Cardiological investigation, carotid angiography, and laboratory testing were normal, including investigation of antiphospholipid antibodies, lipid profile, fasting and post-methionine loading homocysteine concentrations, antithrombin III, protein C, and protein S. The patient was treated with aspirin and did not have arterial ischaemic disease (or venous thrombosis) until now. Resistance to activated protein C (APC) was measured as described[2] and the n-APC-SR was 0.66 (normal>0.84). As expected from this value, the patient was found to be a carrier of the factor V Leiden mutation.[2] Subsequently, she was also shown to be a carrier of the prothrombin 20210 G to A variant[1].

Patient III-37 was admitted at the age of 33 years because of an acute left sided paresis. One year before, she had experienced a transient weakness of the right leg. Otherwise, her medical history was unremarkable (no migraine). She smoked 20 cigarettes a day, did not drink alcohol, and did not take oral contraceptives. She had a left facial palsy, hemianopia, and hemiparesis. Blood pressure was normal. She had no livedo reticularis. Brain CT showed an old left frontoparietal infarct and a recent right frontoparietal infarct. Laboratory investigation, including lipid profile, protein C, protein S, and antithrombin III, cardiological investigation, and carotid angiography were normal. Fasting homocysteine concentration was raised (28.2 µmol/l), without abnormal post-methionine loading concentration. She was treated with aspirin, folate, and pyridoxin and did not have arterial or venous thrombosis until now. APC resistance was normal (n-APC-SR of 1.09), and the factor V Leiden mutation was not present. She was a carrier of the prothrombin 20210 G to A variant.

After informed consent, we prospectively investigated the family members of the probands. DNA testing was not performed in all family members (see pedigree). Medical history of all family members was unremarkable (no ischaemic heart disease, stroke, migraine, or deep venous thrombosis), except for III-39 who had mental retardation, epilepsy, and blindness (she could not be studied). The factor V Leiden and prothrombin variant were investigated in III-34, III-38, III-40, IV-65, IV-66, IV-68, and IV-70. The factor V Leiden mutation was present in III-34 and IV-70, the prothrombin variant in III-40, both variants in IV-65, IV-66, and IV-68, and no mutation in III-38. III-35 (who was not tested) may have both mutations, because her two daughters carry both mutations. III-61 (who is not a relative) probably carries the factor V Leiden mutation, as his wife has the prothrombin mutation, but their daughter has the factor V Leiden mutation. Fasting and post-methionine loading serum homocysteine concentrations were normal in III-34, III-38, III-40, III-41, IV-65, and IV-70.

The occurrence of a stroke in a young person is relatively rare. It is even more rare when two first degree relatives have a stroke at a young age. The second situation strongly suggests a genetic cause, which reduces the list of possible causes considerably.[3] On clinical and radiological grounds and after laboratory and cardiac investigations, in the probands many hereditary causes of stroke were excluded (mitral valve prolapse, atrial myxomas, cardiomyopathies, CADASIL, Sneddon's syndrome, MELAS, and abnormalities of protein C, protein S, and antithrombin III). In homocystinuria thrombotic events are invariably more severe than in our probands, although the occurrence of mental retardation, epilepsy, and blindness in subject III-39 is compatible with homocystinuria (unfortunately, she could not be studied). III-37 had mild hyperhomocysteinaemia, but it is unlikely that this was the (only) cause for her strokes, as hyperhomocystinaemia mostly causes premature atherosclerosis, microangiopathy, and leukoencephalopathy, which were not found. We therefore considered the prothrombotic mutations as the most likely cause.

The factor V Leiden mutation occurs in about 4% of the Dutch population,[2] and the prothrombin mutation in 1% to 2%.[1] The simultaneous occurrence of both mutations in one subject can therefore be calculated as 0.04% to 0.08%—that is, 6000 to 12 000 persons in The Netherlands (about 15 million inhabitants). Nevertheless, so far only one Dutch family in which both mutations occur has been described.[1] All members in this family with both genetic defects experienced venous thromboses.[1] The only other published pedigree in which both mutations occur originates from France.[4] In this pedigree only one subject carried both mutations, and she had recurrent venous thrombosis, but no arterial ischaemic events.[4] The risk for venous thrombosis in patients with both mutations is probably high, as it is known that the factor V Leiden mutation enhances the risk for thrombosis in patients with other prothrombotic states, such as protein S and protein C deficiencies.[5]

Although the association of prothrombotic mutations, such as the factor V Leiden mutation and the prothrombin variant, with