

LETTERS TO THE EDITOR

Treatment of persistent hiccups

Persistent hiccups are difficult to treat and apart from various manoeuvres, drug treatment has included chlorpromazine, haloperidol, nifedipine, and various anticonvulsants. Two patients have been described who responded to baclofen,^{1,2} one of whom had familial hiccups. This letter describes a further patient, whose hiccups followed surgery, who responded dramatically to this treatment.

A man aged 76 years had surgery for left-hip replacement in January 1988. He was troubled with hiccups immediately after recovering from the anaesthetic and the hiccups settled into "ten days on, ten days off" cycles. There was no evidence of neurological deficit when he was examined at that time. He obtained temporary relief by stimulating the back of his throat to the point of vomiting. He was treated with chlorpromazine and then by a variety of anticonvulsants to no effect. Baclofen was then introduced after the cyclic attacks had been continuing for 20 months. At that time he was very distressed and said that he "could not go on". The patient had an immediate response to Baclofen, 5 mg three times daily, but improvement was of short duration and the dose was increased to 10 mg three times daily. The hiccups stopped on the first day of this higher dosage and he was clear for 12 days, when hiccups reoccurred and the dose was increased to 20 mg for three doses. The hiccups then resolved; the dose was reduced to 10 mg four times daily and reoccurred again five days later and lasted for five hours. They occurred six days later and lasted 10 hours and 12 days later when they lasted for 12 hours. The dose of his baclofen was gradually reduced over the following month during which the problem reoccurred for two periods of three hours each. A month later he had hiccups for 30 minutes only. He gradually reduced his tablets to 5 mg and stopped two weeks later, since when no medication has been necessary and no further attacks of hiccups have occurred. The total duration of treatment was three months.

There was an immediate change in the pattern of hiccups on the introduction of baclofen; instead of the bouts lasting about 10 days they continued for only a few hours. Even with these very short periods, they occurred in the same cyclic fashion over the next two months. The attacks have now stopped.

Treatment of persistent hiccups is generally so unsatisfactory that the possible advantage of a trial of baclofen should be added to other possible treatments.

J A GRANT
E M STEINER
Auchterarder, Perthshire
R H JOHNSON
John Radcliffe Hospital, Oxford

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Severe vasculitic neuropathy in systemic lupus erythematosus and response to cyclophosphamide

Neuropathy may be caused by illnesses producing systemic vasculitis^{1,2} including polyarteritis nodosa, rheumatoid arthritis, Wegener's granulomatosis, various forms of granulomatosis and also a more benign non-systemic vasculitic disorder: severe vasculitic neuropathy due to systemic lupus erythematosus (SLE) appears to be very rare.^{2,4} We report a case in which the neuropathy occurred as the predominant clinical feature of a relapse of SLE and which responded to pulses of cyclophosphamide.

Over a period of four weeks, a 24 year old woman, of mixed Philippino and West Indian race, developed night sweats, fever, numbness ascending to the knees and elbows and worsening limb weakness distally and then proximally. SLE had been diagnosed at the age of eight when she developed a rash, fever, haemolytic anaemia, thrombocytopenia and seizures. Subsequently she had episodes of arthralgia and weight loss, splenomegaly and fever, psychosis, proteinuria (renal biopsy consistent with SLE but without vasculitis), and lastly pancreatitis four years previously.

She looked unwell and had a persistent fever of up to 38.5°C. She was alert and orientated. Cranial nerves were normal except for a numb patch corresponding to the left nasociliary distribution. Her limbs were flaccid, areflexic and grossly weak (MRC grading: shoulders 2, hips 2, knees 1 but zero elsewhere). All modalities of sensation were absent to mid-thigh and mid-humeral levels. No other signs appeared during admission except for some livedo reticularis in the hands.

Blood and urine chemistry (including porphyrins) were normal except for a low albumin and raised liver enzymes (bilirubin normal). Haemoglobin was 9.6 g/l (negative direct Coomb's test, "chronic disease" pattern iron studies), white cell count $18.1 \times 10^9/l$ (16.4 neutrophils, 1.45 lymphocytes), platelets 547×10^9 . Bone marrow was normal (including microscopy and culture for acid fast bacilli). ESR was 15 mm/hr, but C-reactive protein (CRP) was grossly elevated at 110 mg/l (normal <10). Microbiological assessment was normal, including blood cultures and serology for Borrelia, Mycoplasma, HIV and other viruses. Complement levels were normal. DNA binding was 56 μ l (normal <25) and ANA titres were >1 in 320 as IgG but only one in 10 as IgM, both with diffuse patterns. CSF pressure, constituents and electrophoresis were all normal.

Nerve conduction studies revealed that compound motor action potentials and sensory action potentials were absent or greatly diminished in all nerves tested, but with normal conduction velocities. A sural nerve biopsy showed acute Wallerian degeneration of axons. One small epineurial vessel had fibrinoid material within its wall, and was also infiltrated by chronic inflammatory cells, as were almost all epineurial vessels.

After 13 days of 40 mg/d prednisolone without any effect, five daily infusions of 500 mg methylprednisolone were given but this had no effect on her clinical condition, fever, CRP or platelet count, though her white cell count and alanine transaminase did return to normal. Prednisolone was then continued at 60 mg per day. Eight days after the methylprednisolone, cyclophosphamide (9 mg/kg) was given intravenously at weekly intervals

for four weeks (each with Mesna cover), without any serious complications, followed by azathioprine (1.5 mg/kg) orally. Her fever settled within 36 hours of the first cyclophosphamide dose, as did her CRP and platelet counts over the next few days. Her power began to improve within three weeks of the first dose, closely followed by a proximal to distal return of sensation. She could walk with the aid of one assistant after six weeks, and independently after six months with foot drop. Arm strength also improved. She continued on azathioprine and a reducing dose of prednisolone. On review one year later, she had marked wasting and weakness in the muscles of her hands, feet and anterior tibial compartment. More proximal power was normal. There was residual loss of proprioception and cutaneous sensation in her fingers and left foot. On repeat electrophysiology, compound motor action potentials and sensory action potentials were again absent or greatly diminished. Conduction velocities were normal or mildly reduced. Electromyography showed signs of denervation in all muscles tested, with signs of reinnervation in all except distal muscles.

Neuropathies in SLE may present as a multiple mononeuropathy, sometimes with a proven vasculitic pathology,⁴ or as a peripheral polyneuropathy,² as in this case. The pathogenesis of this latter distribution may or may not be vasculitic.² In our case the vasculitic nature was suggested by the numb patch in the left nasociliary distribution and confirmed by sural nerve biopsy.

Severe acute peripheral neuropathy in SLE is quite rare and almost always accompanied by evidence of active disease in other organs, including the central nervous system,² though exceptionally it may be the presenting feature.⁴ Coincidental axonal Guillain-Barré syndrome⁵ was excluded by the systemic features, normal CSF protein four weeks into the illness and biopsy findings. The patient appeared unwell and had fever: the laboratory indices of neutrophilia, normal complement levels, normal ESR and raised CRP were contrary to those expected, with little elevation of DNA binding and IgM ANA titres. Her fever, tachycardia and laboratory indices failed to respond to adequate doses of steroids. These features suggested a coincidental infection rather than a flare of SLE, and led to initial caution in the use of immunosuppression.

Whilst a delayed effect of the steroid therapy cannot be discounted, her improvement seemed temporally related to starting cyclophosphamide. The neuropathy showed a delay of about three weeks before improvement was evident, but the other features of her illness settled within a few days. Cyclophosphamide is the preferred treatment of severe vasculitic neuropathy,¹ whose prognosis is otherwise dismal. This patient's impressive response suggests that it may be similarly useful in this rare complication of SLE.

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T P ENEVOLDSON
C M WILES
*Department of Neurology,
St Thomas' Hospital, London*

Correspondence to: Dr Enevoldson, National Hospital for Nervous Diseases, Queen Square, London WC1N 3BG, UK.

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Are alpha-1-antichymotrypsin and inter-alpha-trypsin inhibitor peripheral markers of Alzheimer's disease?

The definite diagnosis of Alzheimer's disease (AD) requires both clinical criteria of probable AD and neuropathological evidence of AD lesions.¹ At present there is no laboratory test for a premortem diagnosis. Recently, genetic and histochemical studies identified protease inhibitors as components that might be implicated in the formation of the amyloid substance in AD brains. First, Abraham *et al*² suggested a potential role of alpha-1-antichymotrypsin (ACT) in the pathogenesis of the lesions, moreover Matsubara *et al*³ found an increased serum concentration of ACT in AD. Second, several authors⁴⁻⁶ showed that one transcript of A4 amyloid precursor contained an additional sequence similar to the active site of inter-alpha-trypsin inhibitor (ITI). The purpose of our study was to test the diagnostic value of ACT and ITI in serum and CSF from AD patients.

Sera and CSF were collected from eight men and 16 women with probable AD,¹ mean (SD) age 66 (9.8) years, and from a control group of 19 men and six women aged 64 (8.3) years. Controls were volunteers free of any neurological disease, with a MMS score higher than 28, who had had a myelo or radiculography for proven disk herniation. CSF was not collected especially for this study. The procedure was approved by the ethical committee of Lille. ACT and ITI contents were measured by electroimmuno-diffusion methods.¹ Semi-quantitative determination was used for ITI in CSF because of its low concentration. Statistical assessment used non parametric tests (Mann and Whitney's U test and Spearman's rank correlation test).

In the control subjects there were 1) no difference in serum or CSF ACT and ITI contents between males and females, 2) no correlation between age and both serum ITI and CSF ACT contents, 3) a positive correlation between serum ACT contents and age ($p < 0.02$).

Between AD patients and controls, there were no difference in serum or CSF ACT and ITI contents, and no difference of the ACT CSF/serum ratio (table).

In AD patients there was no correlation between the severity of dementia on MMS and Blessed scores and serum or CSF ACT contents, and a negative correlation between MMS and Blessed B scores and serum ITI contents ($p < 0.05$).

Our results show that ACT and ITI are not useful markers of AD in serum and CSF. They don't confirm those of Matsubara *et al*.³ The ACT CSF/serum ratio was not significantly modified in AD patients, which is consistent with the hypothesis that the blood-brain barrier is not strongly affected in this disease. The correlation between serum ITI contents and the severity of the dementia could be explained by non specific metabolic disturbances.

ALAIN FURBY
DIDIER LEYS
ANDRE DELACOURTE
LUC BUEE
GUIDO SOETAERT
HENRI PETIT

Departments of Neurology and Neurosciences,
INSERM U156 and ADERMA,
CHRU de LILLE, Hôpital B,
59037 Lille, France

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Postradiation motor neuron syndrome of the upper cervical region—a manifestation of the combined effect of cranial irradiation and intrathecal chemotherapy?

CNS prophylaxis is now an integral part of the treatment of acute leukaemia. We wish to report an unusual case of neurogenic amyotrophy apparently resulting from damage to the anterior horn cells of the upper cervical cord and lower brainstem during cranial irradiation.

The patient presented at the age of 13 in January 1977 with T-cell acute lymphoblastic leukaemia and was treated according to the United Kingdom Acute Lymphoblastic Leukaemia Trial 4 (UKALL 4) (intensive) schedule. This comprised induction with cyclophosphamide, cytosine arabinoside (ara-C), vincristine, prednisolone and intrathecal ara-C; consolidation with the same, together with adriamycin, asparaginase, 6-mercaptopurine, intrathecal methotrexate and cranial irradiation; and maintenance with vincristine, methotrexate, ara-C, 6-mercaptopurine and prednisolone. The total dose of irradiation was 2400 cGy (rads) and the field extended to the level of the C3 vertebral body.

Apart from an early bone marrow relapse in June 1977, he made a complete recovery. In particular, there was no evidence of CNS involvement at any time.

He received his last dose of vincristine in May 1979 and completed his chemotherapy by June 1979. The period of cranial irradiation spanned 19 days in April 1977.

In January 1981 he was referred to the neurology clinic with a three month history of progressive painless wasting and weakness of the shoulder girdle muscles. There was marked bilateral winging of the scapulae, left worse than right. The trapezii, rhomboids, supra- and infraspinati, deltoids, teres major and both sternocostal and clavicular heads of the pectoralis major muscles were wasted, more on the left, and power was reduced to grade 4 on the left and 4+ on the right. There was minimal weakness of the left biceps. The triceps muscles were spared as were the distal upper limb muscles and lower limbs. There was questionable weakness of the orbicularis oculi and failure of frontalis to maintain elevation of the eyebrows. Although his face was thin there was no focal wasting or demonstrable weakness of the other facial muscles. There were no sensory symptoms or signs. Tendon reflexes were well preserved and symmetrical. Plantar responses were flexor.

Investigations at this stage including muscle enzymes, thyroid function, cervical spine radiographs, haematological screen and bone marrow were normal. Electromyographic (EMG) studies revealed reduced amplitude ulnar sensory nerve action potentials and evidence of chronic partial denervation of both deltoids, more on the left.

Thereafter the condition appeared to arrest with no objective progression noted during eight years of follow up (1981-9). Serial EMGs showed evidence of chronic partial denervation and reinnervation in the brachioradialis, biceps, deltoids, supraspinatus and trapezius muscles without pathological activity at rest. No significant abnormality was demonstrated in the quadriceps. In the right tibialis anterior a full interference pattern contained occasional polyphasic units of normal amplitude and duration which were not felt to be of clinical significance. Muscles

Table Serum Alpha-1-antichymotrypsin (ACT) and Inter-alpha-trypsin inhibitor (ITI) contents, CSF ACT contents and ACT serum/CSF ratio in controls group and Alzheimer's disease (AD) patients.

		Controls group	AD Patients
ACT mean (SD)	Serum	0.67 (0.27) g/l	0.63 (0.22) g/l
	CSF	6.97 (1.45) mg/l	7.34 (0.66) mg/l
ITI mean (SD)	Serum/CSF	11.46 (4.5)	12.14 (4.53)
	Serum	0.71 (0.19) g/l	0.72 (0.29) g/l