

chronous myoclonic jerks that affected the face and limbs. Tactile and auditory stimuli produced generalised myoclonic jerks. Fundoscopy and pupillary reactions were normal and oculocephalic, corneal and gag reflexes were present. Muscle tone was normal. Generalised myoclonic jerks were produced when deep tendon reflexes were tested. Both plantar responses were flexor. Formal assessment of muscle power, sensation and coordination was not possible. General examination revealed third and fourth heart sounds and a soft ejection systolic murmur.

Initial biochemical investigation showed: plasma potassium 7.9 mmol/l, bicarbonate 17 mmol/l, urea 47.8 mmol/l, creatinine 1504 μ mol/l, glucose 7.5 mmol/l, arterial blood pH 7.24, pCO₂ 43 mm Hg, pO₂ 104 mm Hg, oxygen saturation 97%. The haemoglobin level was 97 g/l and the leucocyte count $10.8 \times 10^9/l$. Cardiomegaly was present on a chest radiograph. Three sets of blood cultures and a midstream urine specimen were sterile.

Three hours of haemodialysis did not affect the patient's neurological status. A generalised tonic/clonic convulsion occurred less than 10 minutes after administration of naloxone, 0.2 mg. Recurrent hyperkalaemia (7.5 mmol/l) was treated with oral sodium resonium. Electroencephalography revealed generalised theta and delta activity of moderate to high amplitude, intermixed with multifocal spike and sharp waves at a frequency of 1–2 per second. Intravenous injection of clonazepam, 0.5 mg, resulted in immediate cessation of myoclonic jerks and reduction of spike and sharp activity. Lower amplitude semirhythmic 3–4 Hz activity appeared. Myoclonus and hyperkalaemia did not recur. The pethidine level in the plasma stored from the time of admission was <10 μ g/l and the norpethidine level 114 μ g/l. Haemodialysis did not affect the rate of fall of plasma norpethidine levels which were logarithmically related to time (correlation coefficient, $r = -0.82$; $P < 0.05$). The elimination half life of the metabolite in our patient was 25 hours.

The initial metabolism of pethidine occurs in the liver where hydrolysis to pethidinic acid and N-demethylation to norpethidine, followed by hydrolysis to norpethidinic acid, occurs. While repeated administration of pethidine in patients with cancer^{1,2} or sickle cell anaemia⁴ may result in norpethidine accumulation, more rapid accumulation after fewer doses occurs in renal failure. Norpethidine is a central nervous system excitant with less potent depressant effects than pethidine. The progression of

excitatory effects, from nervousness and tremors to agitated delirium, multifocal myoclonus and seizures, in a group of cancer patients treated with pethidine, correlated with the plasma level of norpethidine as well as the ratio of norpethidine to pethidine in the plasma.²

It is likely that the myoclonus and generalised convulsions in our patient were related to norpethidine accumulation. Normal muscle tone and marked stimulus sensitivity do not usually occur in a phenothiazine (prochlorperazine) induced syndrome. In our patient, the effect of uraemia on the threshold for central excitation, resulted in lower norpethidine levels producing myoclonus and seizures compared to the levels required in cancer patients (424–1856 μ g/l).²

In both uraemic and norpethidine related myoclonus, the involvement of not only the distal muscles of the stimulated limb, but also proximal muscles and other limbs in the myoclonic response to peripheral stimuli, suggests that the myoclonus was a reticular rather than a cortical reflex type. The former has been described in uraemia,⁵ hyponatraemia and post anoxic encephalopathy.

Because of norpethidine's long half life in uraemic patients, neurological abnormalities may persist for several days after cessation of pethidine. In the presence of renal failure, repeated muscle contraction may result in life threatening hyperkalaemia and urgent control of myoclonus and seizures becomes necessary. Clonazepam was very effective in this case and is also dramatically effective in controlling post-anoxic myoclonus, where diazepam, phenytoin and phenobarbitone have been ineffective.⁶ In another reported case³ of myoclonus due to presumed norpethidine toxicity, clonazepam was ineffective but the route of administration was not recorded. Naloxone, by completely antagonising the depressant effects of pethidine and norpethidine but only partially antagonising the latter's excitatory effects,⁷ may unmask seizure activity when used in norpethidine intoxication. From our data, norpethidine appears to be difficult to remove by dialysis.

In uraemic patients requiring narcotic analgesia, agents such as pethidine and dextropropoxyphene with toxic metabolites should be avoided. While morphine and codeine may result in unusually severe and prolonged respiratory depression and sedation in renal failure, their cautious use at lower dosage, with careful clinical monitoring, is to be preferred.

We thank Dr G N Thatcher, Nephrologist at Royal Perth Hospital, for giving his permis-

sion to report the case and for reviewing the manuscript.

DAVID C REUTENS
EDWARD G STEWART-WYNN
Department of Neurology,
Royal Perth Hospital,
GPO Box X2213 Perth,
Western Australia 6001

References

- 1 Szeto HH, Inturrisi CE, Houde R *et al*. Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure or cancer. *Ann Intern Med* 1977; **86**:738–40.
- 2 Kaiko RF, Foley KM, Grabinski PY *et al*. Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol* 1983; **13**:180–5.
- 3 Hochman MS. Meperidine-associated myoclonus and seizures in long term hemodialysis patients. *Ann Neurol* 1983; **14**:593.
- 4 Tang R, Shimomura SK, Rotblatt M. Meperidine induced seizures in sickle cell patients. *Hospital Formulary* 1980; **15**:764–72.
- 5 Chadwick D, French AT. Uraemic myoclonus: an example of reticular reflex myoclonus? *J Neurol Neurosurg Psychiatry* 1979; **42**:52–5.
- 6 Jenner P, Pratt JA, Marsden CD. Advances in Neurology, Vol 43: Myoclonus. In: Fahn S *et al*, eds. *Mechanism of action of clonazepam in myoclonus in relation to effects on GABA and 5-HT*. New York: Raven Press, 1986:629–43.
- 7 Gilbert PE, Martin WR. Antagonism of the convulsant effects of heroin, d-propoxyphene, meperidine, normeperidine and thebaine by naloxone in mice. *J Pharmacol Exp Ther* 1975; **192**:538–41.

Intramedullary spinal cord metastasis following a slowly progressive course

Sir: Intramedullary spinal cord metastasis is a well known but rare complication of cancer.¹ In the majority of patients it occurs in conjunction with widespread systemic disease and progresses rapidly.^{2,3} We report a patient in whom the condition was the only indication of relapse and whose signs and symptoms progressed slowly.

A 54 year old woman was referred to our department because of difficulty in walking, burning sensations in the thighs and low backache, slowly progressive over the past year. At the age of 52 an adenocarcinoma of the lung had been detected and a lobectomy of the left lung had been performed.

Examination showed proximal paresis of the legs, MRC grade 3–4/5, more pronounced on the right side. Distally, the strength was nearly normal. Superficial pain and

temperature sensations were disturbed below the level of L2 in both legs. Sensation of vibration was impaired below the hip on the right side and below the knee on the left side. Tendon reflexes of the legs were decreased. Plantar responses were equivocal. Cerebrospinal fluid (CSF) contained 8 leukocytes per mm³; no tumour cells were found at repeated lumbar punctures. The protein and β -glucuronidase content were increased to respectively 1.46 g/l (normal value: 0.20–0.50 g/l) and 37 mU/l (normal value: 9–27 mU/l). Myelography on the first occasion did not show a significant abnormality but three months later showed widening of the spinal cord at level T10–T11. Magnetic resonance imaging (MRI) revealed an intramedullary lesion with prominent enhancement after intravenous administration of gadolinium (fig). Other metastases were not detected and an exploratory operation was performed. After laminectomy, a local tuberosity enlargement of the spinal cord at level T10–T11 was found, with diffuse widening of the spinal cord for two centimeters cranially. The dorsal surface of the spinal cord looked normal and there were no signs of leptomeningeal involvement. After incision, the partly necrotic intramedullary tumour was removed as radically as possible. The histological appearance of the removed tissue was identical to that of the lung tumour. The patient received radiotherapy to the site of the metastasis. Strength and sensation in the legs improved.

For nine months her clinical condition remained stable but the strength in her legs

then declined again. Myelography showed recurrence of the tumour. Radiotherapy induced a second remission for four months after which she developed an almost complete neurological deficit below the level of Th10.

Intramedullary spinal cord metastasis usually has an abrupt onset.³ Untreated, the neurological symptoms evolve within one month to full deficit and more than 80% of the patients die within three months after seeking medical attention.² Our patient and the few other examples published^{3–5} show that the condition can follow a slowly progressive course and hence should be included in the differential diagnosis of a patient with a slowly progressive myelopathy.

As initially in our patient, myelography fails to show an abnormality in about 40% of cases² and MRI is likely to be superior. Patients with intramedullary spinal cord metastasis have variable, sometimes virtually normal, CSF findings.² In some patients it contains identifiable tumour cells but in such cases meningeal carcinomatosis is likely to be present. The slight elevation of β -glucuronidase content noted in our patient may also reflect leptomeningeal involvement, although slight elevations of cerebrospinal β -glucuronidase activities occur with parenchymal metastases.⁶ Radiation therapy can be an effective treatment and lead to neurological stabilisation or improvement and disappearance of pain.³ Operative treatment has been used rarely³ but, as in our patient, can be temporarily beneficial when the condition is slowly progressive.

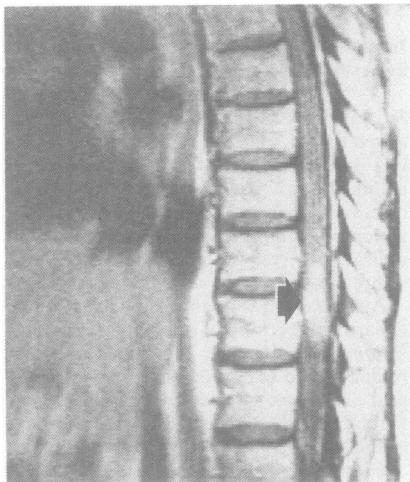


Fig MRI T1 weighted image after intravenous gadolinium showing intense signal intramedullary at T10–T11.

JHJM KOELMAN,*
M DE VISSER,*
JAM KUSTER,†
JJR DREISSEN,‡
J VALK,§
PA KOSTER¶

Departments of Neurology,*
Neurosurgery,‡ Radiology,¶
Academic Medical Centre, Amsterdam
Department of Neurology,†
Elisabeth Gasthuis, Haarlem,
Department of Radiology,§
Free University Hospital,
Amsterdam, The Netherlands

Address for correspondence: Dr JHJM Koelman, Department of Neurology, Academic Medical Centre, Meibergdreef 9, 1005 AZ Amsterdam, The Netherlands.

References

- 1 Costigan DA, Winkelman MD. Intramedullary spinal cord metastasis. *J Neurosurg* 1985; 62:227–33.

- 2 Grem JL, Burgess J, Trump DL. Clinical features and natural history intramedullary spinal cord metastases. *Cancer* 1985; 56:2305–14.
- 3 Winkelman MD, Adelstein DJ, Karlins N. Intramedullary spinal cord metastases: diagnostic and therapeutic considerations. *Arch Neurol* 1987; 44:526–31.
- 4 Smalino F, Bernini FP, Santoro S. Computerized tomography in the diagnosis of intramedullary metastases. *Acta Neurochirurgica* 1980; 52:299–303.
- 5 Murphy KC, Feld R, Evans WK, et al. Intramedullary spinal cord metastases from small cell carcinoma of the lung. *J Clin Oncol* 1983; 1:99–106.
- 6 Zanten AP van, Twijnstra A, Benthem V van, et al. Cerebrospinal fluid β -glucuronidase activities in patients with central nervous system metastases. *Clin Chem Acta* 1983; 147:127–34.

Since this paper was accepted an additional article describing the value of gadolinium-enhanced MRI in the diagnosis of intramedullary metastases has appeared: Fredericks R, Elster A, Walker FO. Gadolinium-enhanced MRI: a superior technique for the diagnosis of intraspinal metastases. *Neurology* 1989; 39:734–6.

Management of intraventricular haemorrhage secondary to ruptured arteriovenous malformation in a child with Von Willebrand disease

Sir: We report a case of an adolescent female who presented with intraventricular haemorrhage following minor trauma. The patient was diagnosed as having von Willebrand disease but, in addition, had an intracerebral arteriovenous malformation. This case emphasises the need to investigate possible structural abnormalities even in the presence of a known coagulopathy in patients with intracerebral haemorrhage.

A 13 year old female complained of headache, nausea, vomiting, stiff neck and blurred vision two days after a minor episode of head trauma. CT revealed intraventricular and subarachnoid haemorrhage. She also reported a history of heavy menstrual flow and epistaxis while taking aspirin. Her family history was notable for easy bruising and prolonged bleeding. Apart from meningismus, neurological examinations were normal. Coagulation studies revealed normal prothrombin and partial thromboplastin times but a prolonged bleeding time. The diagnosis of type 1 von Willebrand's disease was ultimately made. Following a bolus cryoprecipitate she was placed on a continuous cryoprecipitate infusion, titrated to keep her von Willebrand's factor greater than 50%.