LETTERS TO
THE EDITOR

MRI appearances in subacute combined degeneration of the spinal cord due to vitamin B12 deficiency

The dorsal columns of the spinal cord are recognised on both clinical and pathological grounds to be particularly vulnerable to demyelination in subacute combined degeneration associated with vitamin B12 deficiency.1 We report the MRI findings in a patient with subacute combined degeneration associated with pernicious (addisonian) anaemia.

A 38 year old man complained of a two month history of numbness in the tips of his fingers leading to difficulty with writing and doing up buttons. His neck was painful and he noted that neck flexion produced tingling sensations in his hands. Symptoms progressed over the next six weeks to include numbness of the toes and the right side of his chest. Clinical examination at this time disclosed pronounced pseudoathetosis with loss of distal joint position sense and vibration sensation in the upper limbs, but temperature and pin prick sensation were preserved. Both Lhermitte's and Romberg's signs were positive. Tone in the limbs was normal except for a spastic catch in the left arm. Reflexes were generally brisk with bilateral crossed adductor responses, but the ankle jerks could only be obtained with reinforcement. The right plantar response was extensor. Premature greying of the hair was noted.

Laboratory studies showed a macrocytic hyperchromic anaemia (haemoglobin 118 g/l, normal range (NR) 130-180 g/l; mean corpuscular volume 120±8 fl, NR 76-90 fl; mean corpuscular haemoglobin 39-9 pg, NR 27-32 pg) and hypersegmented neutrophils were seen on a blood film. Serum vitamin B12 concentration was low at 342 ng/l (NR 150-900 ng/l) and red cell folate concentrations were normal (339 µg/l; NR 130-850 µg/l). Intrinsic factor antibodies were positive, indicative of pernicious anaemia, and gastric parietal autoantibodies were weakly positive. A Schilling test (DICOPAC) showed a very high ratio of 58Co to 57Co in a 24 hour urine collection after an oral dose of tetracycline labelled vitamin B12 (9.8%); normal range 0.8-1.3), only 2.8% of the dose being excreted in the urine (NR > 11%). This indicates impaired gastromesenterial absorption of vitamin B12. Analysis of CSF was normal, as were visual evoked responses and nerve conduction studies.

Studies with MRI showed slight but definite swelling of the upper cervical cord on the T1 weighted sequence (fig 1), and a strikingly high signal was seen posteriorly within the cord on T2 weighted images (fig 2) extending from the C1 to the C5 vertebral level. This lesion showed no contrast enhancement. No other abnormality was detected within the spinal cord or brain. The patient was treated with 1 mg intramuscular injections of hydroxycobalamin, initially weekly for a month and then at intervals of three months. On this regime his clinical symptoms and signs resolved, and haematological variables returned to normal. Repeat MRI at six month follow up was normal.

Few reports and illustrations of the MRI findings in subacute combined degeneration have appeared.2,3 In most patients reported, vitamin B12 deficiency has been secondary to pernicious anaemia, but cases after gastrectomy4 and chronic atrophic gastritis5 have also been reported. Generally T2 weighted scans have demonstrated focal high signal abnormalities in the white matter of the dorsal and posterior columns. Some reports have shown preferential involvement of the dorsal columns, in keeping with the reported symptomatology.6,7 These changes may be confined to a few segments or may extend throughout the length of the cord.8 The radiological changes have resolved over several months, concurrent with correction of B12 deficiency with hydroxycobalamin treatment, in all but one patient.9 Gadolinium had been given to only one patient previously, and produced mild enhancement.10

The value of MRI in the differential diagnosis of intramedullary causes of myelopathy is well established.11 The differential diagnosis is broad, including demyelination, malignant lymphoma and other neoplasia, HIV myelopathy, syringomyelia, and subacute combined degeneration. Demyelinating plaques seldom exceed two vertebral bodies in length and are multiple in 50% of patients. A normal brain scan also makes demyelination unlikely. Acute transverse myelitis, cord ischaemia (posterior spinal artery syndrome), and postradiation myelopathy can all be excluded on clinical grounds. The paucity of enhancement with gadolinium argues against cord neoplasia, and granulomatous and infective processes.

Our findings suggest that MRI may be used in conjunction with clinical assessment to monitor the efficacy of treatment in subacute combined degeneration, particularly in patients with no concurrent haematological abnormality.

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Figure 1 T1 weighted MRI (sagittal section) of the cervical cord, showing slight prominence of the upper cervical cord.

Figure 2 T2 weighted image of the same area as in fig 1, showing a high signal intensity lesion posteriorly within the cervical cord, extending from C1 to mid-C5.

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Rapid neurological deterioration in a patient with multiple sclerosis treated with systemic interleukin-2 and interferon-α 2b for metastatic renal cell carcinoma

Previous case reports documented reactivation of psoriasis and rheumatoid arthritis in patients treated with systemic interleukin-2 for malignant conditions. We now report rapid worsening of another immune mediated disease multiple sclerosis in a patient with secondary progressive multiple sclerosis and metastatic renal cell carcinoma treated with systemic interleukin-2 (IL-2) and interferon-α (IFN-α). Although IL-2/INF-α therapy temporarily accelerated the rate of progression of multiple sclerosis, the antitumour response was complete. This case highlights the potential role of IL-2 in the progression of neurological deficits in patients with multiple sclerosis. Clinicians and patients should be prepared for this potential complication, and studies employed to help clarify the mechanism(s) involved.

A 57 year old woman had developed relapsing-remitting symptoms of multiple sclerosis in 1983. Between December 1988 and 1991 she experienced a progressive decline in function without exacerbations. Yearly brain MRI documented new lesions in all studies and gadolinium (Gd) enhancing lesions in two of the three studies.

In October 1991 renal cell carcinoma of the right kidney was diagnosed with metastases to the distal right femur and right lower lobe of the lung. Neurological examination six weeks after total knee arthroplasty and immediately before starting IL-2/INF-α therapy showed 20/20 visual acuity, optic disc pallor, a partial right internuclear ophthalmoplegia, mild upper limb dysfunction (by nine hole peg testing) with normal strength, a moderate paraparesis, and an ability to walk comfortably with a walker.

On 10 February 1992, she began a 25 day course of therapy with rIL-2 at a dose of 0.5 mg/m²/24 h by continuous intravenous infusion and rIFN-α at a dose of 15 million units subcutaneously every Monday, Wednesday, and Friday. Three hours after the initiation of treatment she developed a temperature of 38°C, nausea, vomiting, lethargy and muscle spasms. Urinalysis and culture disclosed a urinary tract infection, and treatment was initiated with ciprofloxacin. The next day her temperature was normal, and her symptoms resolved while the rIL-2 infusion was continued. She remained afibrile and signs of toxicity subsided, except for a subtle erythematous rash and mild myalgia. Three days after beginning IL-2/INF-α therapy, her neurological condition began a rapid and progressive deterioration without associated fever. Neurological examination one week after beginning treatment disclosed paraplegia with moderate weakness of the upper limbs, bilateral acuity of 20/100 OD and 20/50 OS, and a complete right internuclear ophthalmoplegia. She was admitted to the hospital and IL-2/INF-α therapy was discontinued. Brain and spinal cord MRI showed no evidence of metastasis, Gd enhancement, or increase in multiple sclerosis lesion burden. Serial MRI was performed and quantified according to a standardized protocol to document the progression of disease over time. Analysis of CSF showed increased intrathecal IgG synthesis without any pleocytosis or evidence of breakdown of the blood-brain barrier. Three days after discontinuation of IL-2/INF-α therapy, visual acuity had improved to 20/20 in both eyes and she had antigravity strength in the left leg. She remained unable to stand, transfer independently, or walk. After another three days off therapy, she was restarted at a 50% dose reduction. Repeat neurological examination on the last day of IL-2/INF-α and 10 days later showed no change from the examination on 21 February 1992.

She received a second 25 day course of IL-2/INF-α therapy (23 March to 18 April), at a 50% dose reduction, followed by a right first metatarsal nerve block. Neurological examination one week after operation showed significant progression of left leg weakness and atrophy of intrinsic hand muscles. Brain MRI six weeks after operation showed no Gd enhancement or increase in plaque load. The patient remains in remission from renal cell carcinoma four years after IL-2/INF-α therapy.

Whereas the precise mechanism for neurological deterioration in this case remains uncertain, we propose that treatment with IL-2 focally accelerated immune mediated demyelination without formation of new multiple sclerosis plaques. Systemic immune activation was precipitated by complications in a case of fatal encephalomyelitis beginning four days after the initiation of IL-2 therapy, in a neurologically normal patient with metastatic renal cell carcinoma. Histopathological changes of acute perivascular inflammation and a CSF formula consistent with breakdown of the blood-brain barrier were demonstrated in this case. These features would be expected in acute inflammatory demyelination, which requires breakdown of the blood-brain barrier and recruitment of systemic mononuclear cells into the brain. By contrast, chronic active plaques in patients with progressive multiple sclerosis already contain the necessary T cells, antigen, antigen presenting cells, and costimulatory signals for further demyelination.

Administration of exogenous IL-2 could theoretically accelerate this process, through in vivo stimulation of activated T cells and macrophages, without producing a significant change in the appearance of standard T2 weighted or gadolinium enhanced MRI. This hypothesis may be tested in the future by employing magnetic resonance spectroscopy and magnetic transfer imaging to directly assess the number of plaques formed after myelin breakdown products and demyelination respectively.

Despite our patient’s neurological deterioration, she experienced a gratifying antitumour response to systemic IL-2/INF-α therapy. Until clinicians gain further experience with IL-2 therapy in patients with multiple sclerosis, decisions to initiate treatment must be made empirically based on the patient’s optimal functional status.

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A rostrocaudal gradient of nitrate plus nitrite concentrations in CSF

Lumbar CSF concentrations of nitrate plus nitrite are increasingly being used to investigate neurological disease and injury. These stable breakdown products of nitric oxide and the peroxynitrite anion and alterations in their concentrations in CSF are assumed to reflect nitric oxide synthase activity in the brain. This is some experimental evidence to support this.

We have recently reported an age related decrement in the concentration of CSF nitrate plus nitrite in a paediatric reference population aged between 0 and 9 years. Our method of collection of CSF is standardised and collects a fixed volume of fluid (the third 1 ml is used for nitrate plus nitrite concentrations) regardless of the size of the child. This means that the shorter the child, the more rostral the sampling site. To determine whether there is a rostrocaudal gradient for CSF nitrate plus nitrite we have reanalysed the data taking into account the length or height of the child.

There was a better inverse correlation between log concentrations (nitrate plus nitrite) and height (r = -0.65, P < 0.001) than between log concentrations and age (r = -0.27, P = 0.677). This height was taken into account in a partial correlation analysis, there was no longer any relation between log concentrations (nitrate plus nitrite) and age (r = 0.07, P = 0.76). Because the lumbar CSF is thought to act as a sump in humans, this finding indicates a rostrocaudal gradient in CSF nitrate plus nitrite concentrations. In turn, a rostrocaudal gradient implies that lumbar nitrate is generated higher in the neuraxis than the lumbar sac, which provides indirect evidence that lumbar CSF nitrate plus nitrite is generated in the brain and is not causally related to the breakdown of nitric oxide.

These findings do not, however, detract from the use of appropriate reference inter-
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