Destructive lesions in demyelinating disease

Bryan D Youl, Allan G Kermode, A J Thompson, T Révész, F Scaravilli, R O Barnard, F J Kirkham, Brian E Kendall, Derek Kingsley, Ivan F Moseley, J M Stevens, C J Earl, W I McDonald

Abstract

Three cases are presented in which clinical and radiological features suggested the diagnosis of glioma but surgical biopsy revealed a demyelinating process, with tissue destruction and cyst formation in two. One patient had clinically definite multiple sclerosis. Two had probable acute disseminated encephalomyelitis. Treatment with high dose steroids is appropriate when there is clinical or investigative evidence to suggest the presence of demyelinating disease, before deciding on biopsy.

Diagnostic difficulty may arise when patients suspected of having demyelinating disease develop evidence suggesting tissue destruction clinically, radiologically, or at biopsy. A similar difficulty arises when there is radiological evidence of swelling of nervous tissue, most commonly in the spinal cord, and more frequently detected since the advent of MRI. Since physicians are often concerned that the apparent development of tissue destruction may be incompatible with a diagnosis of demyelinating disease, we report the clinical, radiological and histological findings in three such cases, one of multiple sclerosis (MS) and two who probably had acute disseminated encephalomyelitis (ADEM).

Case reports

Case 1

A 16 year old male student developed left hand numbness in May 1986. This extended to the entire left side of the body and then resolved over two months. Four months later the numbness returned, now accompanied by left hand weakness, unsteadiness of gait, impaired hearing in his left ear, occipital headache and visual disturbance. There was severe left facial weakness, nystagmus on left lateral gaze and left sensorimotor deafness. Limb power was normal but the plantar responses were extensor. There was incoordination in the left arm and leg and impaired joint position sense in the fingers of the left hand.

A contrast enhanced CT head scan was normal. Pontine glioma was suspected but an MRI examination of the head showed numerous discrete and peri-ventricular high signal lesions within the white matter of both cerebral hemispheres on a T2-weighted sequence. There were further abnormal regions in both cerebellar hemispheres and in the left side of the pons. There was also a small region of high signal adjacent to the right frontal horn.

The patient was admitted. The CSF was clear—31 leukocytes per mm³ (97% lymphocytes, 3% macrophages), protein 0·68 g/L, glucose 3·8 mmol/L (serum 5·3 mmol/L). Oligoclonal IgG bands were present; serum was not tested. High dose intravenous methylprednisolone was given. His symptoms improved over the following week so that on discharge his hearing was normal and the facial weakness was less severe. Slight incoordination of left arm movement persisted.

He remained well until the 3 February 1987, nine months after the original illness, when he developed headache and generalised myalgia. Cotrimoxazole was given. A week later he complained of progressive disturbance of vision and balance, so that five days later he was unable to walk. He was also drowsy. On examination there was an internuclear ophthalmoplegia and first degree vertical nystagmus. There was ataxia in the left upper limb and left upper motor neuron seventh cranial nerve palsy with generally brisk deep tendon reflexes and extensor planter responses. Tone was increased in the lower limbs.

He was admitted to the National Hospital, where intravenous methylprednisolone was administered (500 mg daily for five days). There was a transient improvement, but by mid March he was again severely disabled. A second course of corticosteroid was given and azathioprine was started (50 mg three times daily). His neurological state improved but in the second half of April he began to vomit episodically. CT on the 13 May showed a large ring enhancing lesion with mass effect and some surrounding oedema in the right frontal lobe (figs 1a and b).

Cerebral abscess was suspected, but two days later, on aspiration via a burr hole, the lesion was found to contain clear xanthochromic fluid. Cytological study was negative for neoplastic cells. A right frontal craniotomy was carried out 10 days after the first procedure. The cyst wall was removed, together with the surrounding abnormal tissue on the assumption that this was a glioma.

Histology showed an area of complete myelin loss which included the wall of the cyst. The area was separated from the cortex by a thick rim of apparently normal white matter. The border between normal and abnormal myelin was sharply demarcated by a
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Figure 1 13/5/87 Axial CT sections (a) plain and (b) after intravenous contrast medium. There is a large low density lesion which shows mass effect with a higher density rim which enhances. There is a small amount of surrounding oedema.

complete loss of myelin sheaths and by an increased number of cells. These included astrocytes and elongated, radially arranged cells which reacted with the antibodies to macrophages to form a palisade at the border with the normal myelin. Inside the area of myelin loss, there were increased numbers of both astrocytes and blood vessels. There were numerous macrophages which became proportionally more numerous towards the centre of the lesion and, on frozen sections, appeared to be filled with neutral fat.

The blood vessels were cuffed with chronic inflammatory cells, predominantly lymphocytes. These reacted positively with leucocyte common antigen and most of them appeared to be T-cells. Within the abnormal area the density of axons was greatly decreased, however, they were seen among the large amounts of astrocytes and macrophages and tended to become sparse only at the centre of the lesion. The leptomeninges showed no significant abnormality. Immuno-histochemical staining for anti-glial fibrillary acidic protein revealed that the myelin surrounding the lesion contained a number of reactive astrocytes which were also present, in decreasing numbers, in the lower layers of the cortex.

In summary, the appearances were not those of a tumour, but of a subacute demyelinating lesion compatible with a plaque of multiple sclerosis. Phenytoin (300 mg daily) was started. His clinical state improved and azathioprine was withdrawn. On the 2 June 1987 he was able to walk without assistance. Eye movements were full. There was first degree nystagmus on gaze to the left and mild incoordination of the left upper limb and both lower limbs. The deep tendon reflexes remained brisk but the plantar responses were flexor. He has since had generalised seizures approximately monthly but has been otherwise well.

The history of relapsing and remitting neurological disturbance and the presence of multiple CNS lesions on MRI led to a diagnosis of MS which was supported by finding oligoclonal bands in the CSF. The histological findings confirmed the diagnosis.

Case 2

A 19 year old male accountant was admitted to another hospital on 20 February 1988. Three weeks earlier he had developed right hand weakness which progressed over two weeks to affect the entire limb, producing complete paralysis. There was pain over the upper thoracic vertebrae. Two days before admission he noticed slight weakness of the right lower limb and developed urinary retention. He had been well previously but recalled having had a "cold" with rhinorrhea and myalgia several days before the onset of neurological symptoms. There had been no headache.

On examination he was unable to stand. Intellectual function, speech and ocular fundi were normal. There was slight lower right facial weakness and complete paralysis of the right upper and lower limbs with hypotonia but preservation of deep tendon reflexes. The left upper limb was normal but there was mild weakness in a pyramidal distribution in the left lower limb, with normal tone and deep tendon reflexes.

CT showed a high left frontoparietal lesion which enhanced in a ring pattern with contrast but exerted no mass effect. The patient was transferred to the Maid Vale hospital on 25 February, where a left carotid angiogram via the right femoral artery demonstrated an avascular region which occupied most of the left parietal lobe and extended anteriorly beyond the coronal suture. No tumour vessels were seen. Corticosteroid therapy was started (methyl-prednisolone 500 mg daily iv).

Glioma was suspected and a burr hole biopsy was carried out on the same day. Cyst fluid was aspirated which contained 7000 erythrocytes and 460 leukocytes per mm$^3$ of which 58% were macrophages, 17% polymorphs and 25% lymphocytes. The protein content was 50 grams per litre. Microscopy and culture were negative.

Histology showed that the tissue samples from the cyst wall were devoid of neoplasm. The cerebral cortical areas present were well preserved. In the underlying white matter features of myelin breakdown, a large number of foamy histiocytes and also sparse and damaged axons were seen. There was extensive perivascular lymphocytic cuffing around some of the venules. The inflammatory cells were found to be a mixture of B and T lymphocytes and also macrophages. The astrocytic reaction was marked throughout and some multinucleate astrocytes were also seen. The histological appearances were compatible with an acute demyelinating process.

Visual and auditory evoked potential studies were normal post-operatively but there was absence of the post-central N20 component and enhancement of the pre-central P22 component on stimulation of the right median
nerve. T2-weighted MRI examination (Picker 0-5 T) showed a large region of high signal at the site of the biopsy in the left parietal white matter with a central area of lower signal (fig 2a). This extended to, but spared the grey matter. T1-weighted inversion recovery sequences (fig 2b) showed that the lesion returned non-uniform low signal with a central area of still lower signal, consistent with central necrosis. There was a further small lesion in the right parietal white matter.

The patient improved slowly on a decreasing dose of oral dexamethasone, but on the 5 April, 40 days after surgery, the left lower limb became weaker and he developed a right T6 and left T8 spinthalamic sensory level. Power improved on increasing the dose and the sensory loss became more patchy. He remained in urinary retention.

T1-weighted MRI examination of the spinal cord (12 April 1988) showed focal swelling at C2 and T2-3 levels and there was diffuse increase in the enlarged segments on T2-weighted images. Lumbar puncture yielded clear CSF-3 WBC/\mu L, protein 0-75 g/L, glucose 2-2 mmol/L (4-0 mmol/L in serum). Oligoclonal IgG bands were not detected. He returned to the referring hospital two months after admission to Maidan Vale.

Dexamethasone was gradually withdrawn and his symptoms improved over the following six months; the urinary catheter could be removed after two months. MRI examination nine months after surgery showed a marked reduction in the size of the left parietal lesion and disappearance of the right parietal lesion. In the spinal cord, the swelling had resolved and the signal abnormalities had diminished. By January 1989, the only abnormal finding was a mild right hemiparesis.

The history of a systemic illness followed by a clinical picture characterised by cerebral and spinal symptoms suggests a diagnosis of acute disseminated encephalomyelitis (ADEM). MS cannot of course be excluded, but the absence of oligoclonal bands in the CSF and the striking clearing of the MRI lesions are more in keeping with the former. It is not clear whether the development of new spinal symptoms when the steroids were reduced represents a true relapse or not; thoracic pain had been a prominent symptom at the onset but spinal cord imaging was not performed until the sensory level appeared. Even if this were a relapse the diagnosis of ADEM is not excluded after such a short interval.2

Case 3

A 36 year old Singaporean female of Chinese descent was well until October 1988, when mid-way through her first pregnancy. Over several days she developed mild neck discomfort, palmar and plantar numbness and tightness about her lower thorax. Her hands were intermittently weak. In December her pregnancy spontaneously aborted. The symptoms persisted. On the 4 March 1989 she developed mild fever with generalised myalgia and felt unwell. A pregnancy test was positive. On the 8 March the numbness extended for the first time to involve the right lower limb to the groin. As she walked the buttocks and left lower limb became affected. On the 11 March her legs stiffened and she was unable to walk.

She was admitted to hospital in Singapore on the 13 March. T1-weighted MRI examination (GE 0-5 T) showed swelling of the cervical cord from C2 to C6 (fig 3a) with central, well-defined low signal regions (fig 3b). Scans of the head were reported as normal. The next day she had a laminectomy (C2 to C5) and cord biopsy on the assumption that the swelling was due to a tumour, and the pregnancy was terminated. There was no change in her symptoms. Histology was thought initially to be consistent with astrocytoma. Corticosteroid therapy was started and she was transferred to a hospital in the USA for radiotherapy, where a further MRI examination showed her cervical cord to be of normal dimensions. Revue of the histological material led to a revised diagnosis of either infarction or demyelination. Spinal angiography was normal. A CSF specimen showed a single abnormal band in the gammaglobulin region.

Her symptoms progressively improved. Medication was withdrawn in mid-April and she was discharged. On the 5 of May she developed further fever, headache and nausea. These symptoms resolved over 48 hours but she went on to develop urinary retention on the 14 May whilst flying back to Singapore.
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The first MRI head scan was reviewed. Many small areas of high signal, discrete from the ventricles, were seen within the white matter of the cerebral hemispheres on T2-weighted sequences. New histological preparations were prepared from the spinal cord biopsy material. Tissue was stained with haematoxylin and eosin, haemotoxylin—van Gieson, Glee and Marsland silver impregnation for axons and luxol fast blue/cresyl violet.

Histology showed a small fragment of tissue consisting of macrophages arranged in sheets and rows intermingled with less numerous reactive astrocytes. Macrophages were uniformly round or polyhedral with small peripheral nuclei and finely vacuolated cytoplasm. Astrocytes had abundant homogeneously eosinophilic cytoplasm and peripheral nuclei. Myelin stains revealed no myelin. The silver stain, however, revealed moderate numbers of surviving axons. A small number of blood vessels was included in the specimen. These were not cuffed by inflammatory cells. The histological appearances suggested a subacute/chronic demyelinating process.

The ACTH injections were replaced by a 120 mg alternate day oral prednisolone regimen. Her condition began to improve steadily, and the medication was gradually withdrawn over six months. Eight months later there had been no relapse.

As in case 2, MS cannot be excluded after so short a follow up, particularly since in Orientals the lesions of MS tend to be more destructive than in white groups. On the other hand, the numerous small hemispheric lesions sparing the periventricular region would be unusual in MS. This feature and the disappearance of the monoclonal band are more in keeping with a diagnosis of ADEM, even though the history of a preceding systemic illness is not clear. The two relapses within seven months are in keeping with the course of ADEM described by Miller and Evans.

Discussion

The occurrence of marked swelling in cases 1 and 3 and ring enhancement at CT in case 2 raised the question of glioma and the presumptive diagnosis of tumour led to surgical intervention in all three cases. The histological investigation, however, excluded neoplasia and led to the identification of the infrequently recognised association of extensive tissue destruction with MS and ADEM.

There are many reports of cases of demyelinating disease where CT scan has shown lesions exhibiting both mass effect and contrast enhancement, though tissue necrosis is rarely seen at necropsy in MS. Two reports are of particular interest in relation to our patients. Harpey et al documented the case of a 14 year old male who presented with the rapid onset of right hemiplegia. CT revealed a large left temporoparietal lesion which exerted a mass
effect and showed a ring pattern of contrast enhancement. Neo-vascularisation was not seen at cerebral angiography. A cystic lesion was exposed at surgery and removed. Pathological examination showed a necrotic process with cellular infiltration of white matter, with perivascular lymphocytic cuffing and relative preservation of axons. Three months later the patient presented again, with paraesthesiae and weakness of the left upper limb. CT now showed a second lesion, contralateral to the first. This new lesion enhanced with contrast whilst the first no longer did so. The patient improved with steroid therapy and recovered to the extent of having only mild right hemiparesis 40 months after the onset of symptoms. Secondly, Hunter et al. examined surgical biopsy specimens from four patients with probable MS in whom clinical and CT findings had suggested cerebral neoplasia. In all cases the lesions consisted of sheets of gemistocytic astroglia interspersed by numerous foamy macrophages, in the absence of associated necrosis. There was total destruction of myelin sheaths with relative preservation of axons. Significant inflammation was present in only one specimen.

Necrosis may be seen in other demyelinating diseases. It is commonly described in the syndrome of neuromyelitis optica in which capillary proliferation with cavitation has been observed. This syndrome is probably a variant of MS and is relatively more common in Orientals than in European whites. Necrosis in the classical form of MS also appears to be relatively frequent in orientals. It also occurs in concentric sclerosis and centrolateral sclerosis (Schilder’s disease).

Adams and Kubik have also reported necrosis in ADEM in a 24 year old male who presented with a fulminant spinal cord syndrome associated with fever, who died 13 days later. The cervical cord was found to be soft and haemorrhagic. Meningitis and perivascular and sub-pial demyelination were present in the spinal cord, medulla and pons. Small blood vessels in the cervical cord were necrotic. A similar case was described by De Busscher and Radermecker in which fever had not been prominent.

The mechanism of necrosis in demyelinating disease is uncertain. Roizin et al. suggested that it resulted from oedema and swelling occurring in and around the active plaque. More speculatively, Adas proposed that either multiple sclerosis is not an obligatory demyelinating disease (and that, if the process is sufficiently cytotoxic, a lesion focally resembling a necrotising encephalomyelitis may arise), or that secondary thrombosis in vessels in and around a plaque may promote ischaemic necrosis. Whatever the mechanism, the end result of the necrotising process is cyst formation, the cavity being surrounded by fibrous glia and traversed by a network of connective tissue. It is thus clear that tissue necrosis can occur in a variety of demyelinating diseases, and should be suspected when cystic change is demonstrated by MRI or CT in patients with known demyelinating disease. On the basis of our experience, we suggest that when a patient has evidence of a cyst or swelling of the brain or spinal cord with rapid progression of neurological dysfunction in association with clinical or investigational evidence of MS, early biopsy should be avoided and the patient treated with high doses of steroids. The same policy should be adopted in patients with acute neurological illness with features suggesting ADEM. If the patient fails to respond after a reasonable interval, biopsy should be considered.

NOTE ADDED IN PROOF

We have since seen three further cases of necrotic lesions in a setting of clinically definite MS (two cases) and ADEM (one case) in whom suspicion of tumour has led to biopsy.

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