SHORT REPORT

Fulminant monophasic multiple sclerosis, Marburg's type

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Abstract

The clinical, neuroradiological and necropsy findings are described in a 49 year old woman with long-standing idiopathic pulmonary haemosiderosis and acute monophasic multiple sclerosis (Marburg's type). Progression of the demyelinating process produced blindness and paraplegia over three weeks. At five weeks, magnetic resonance imaging (MRI) studies showed lesions in the pons and left occipital lobe. The patient died 10 weeks after onset of symptoms. Necropsy examination revealed acute plaques in the optic chiasm, and the white matter around the lateral and fourth ventricle and spinal cord. Similarities between this and previously described cases of Marburg's disease are discussed.

Marburg's disease, an acute, fulminant, monophasic variant of multiple sclerosis remains incompletely characterised.^{1,2} Recognition of this entity may be hindered by the absence of previous neurological symptoms, a fulminant course and necropsy evidence of extensive axonal loss, and necrosis.^{1,2}

Case report

A 49 year old white woman with idiopathic pulmonary haemosiderosis was admitted to the hospital for investigation of right facial numbness lasting five days and associated with tingling and numbness of the left upper and lower extremities. Three weeks earlier she had an episode of blindness lasting about one minute.

Four years earlier she started having episodes of extreme fatigue associated with anaemia (haemoglobin as low as 6.0 g/dl) and pulmonary infiltrates, but neither fever nor rigors. Idiopathic pulmonary haemosiderosis was diagnosed by lung biopsy two months before admission, and treatment with prednisone (40 mg daily) was started.

On examination, stimulation of the skin of the left leg with a sharp object, elicited tingling; the remainder of her neurological and general examinations were normal. Biochemical and haematological blood tests were normal. A head CT scan with and without

contrast was normal. A chest radiograph showed mild diffuse bilateral interstitial fibrotic changes with evidence of old granulomatous disease. An echocardiogram demonstrated mild mitral valve prolapse.

The following day she developed blurred vision. She had a right gaze palsy and a right internuclear ophthalmoplegia (one and a half syndrome), and a mild right lower motor neuron facial paresis. An MR head scan that day showed an area of increased T2 weighted signal in the right posterior pons, crossing the midline, with slight compression of the fourth ventricle. CSF examination demonstrated an opening pressure of 120 mm CSF, with 40 white cells/cumm (98% neutrophils), 24 red blood cells/cumm, protein 33 mg/dl, glucose 57 mg/dl. Gram stain and cultures were normal. The following day she complained of difficulty in swallowing and walking. Her neurological examination was unchanged except for bilateral extensor plantar responses. Cyclophosphamide 100 mg orally daily was started. Four days after admission she complained of mid-back pain, developed complete urinary retention and within three hours of the onset of the pain, a flaccid paraplegia with a sensory level of T8. Dexamethasone, 20 mg intravenously, was administered and a regime of dexamethasone, 10 mg six hourly began. A complete myelogram was normal. A further head CT was normal as was a CT of the lumbar spine. Cerebrospinal fluid from that examination demonstrated 5150 white cells/cumm (89% neutrophils), RBC's 610/cumm, glucose 26 mg/dl, and protein 394 mg/dl. Ceftriazone 2 g IV 12 hourly was administered.

Eight days after admission though still alert and oriented with a persistent one and a half syndrome and vertical ocular flutter, she developed reduced sensation to noxious stimuli in the distribution of all three divisions of the left trigeminal nerve, weakness in the motor division of the right trigeminal nerve, right Horner's syndrome, right peripheral facial palsy, and deviation of the tongue to the left. She had mild weakness and hyperreflexia of both upper limbs worse on the left, with a flaccid paraplegia, absent reflexes in the lower limbs and a cord level now to the second thoracic dermatome. Shortly afterwards, she suddenly went blind; her visual acuity was limited to hand movement and finger counts, with bitemporal

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Figure Representative lesions. (A) Magnetic resonance image showing an increased T2 weighted periventricular signal in the pons. (B) Pons showing periventricular demyelination of dorsal plaque depicted in A (Mahon myelin stain, magnification $\times 5$). (C) Extensive infiltration by lipid-laden macrophages and perivenular lymphocytic cuffing in acute pontine plaque (haematoxylin and eosin, magnification $\times 72$). (D) Edge of concomitant acute optic nerve plaque exhibiting demyelination, moderate axonal loss and an extensive macrophage infiltrate (Mahon myelin stain, magnification $\times 22$).

hemianopia to confrontation, poor pupil responses with light near dissociation, and a right relative afferent pupillary defect. Fundoscopic examination was normal. Cerebral arteriography was normal. An exploratory craniotomy was performed: the optic nerve chiasm and arachnoid appeared normal; the cerebral cortex had a granular appearance. Histological examination of material taken from the optic chiasm and temporal lobe revealed prominent arachnoid thickening compatible with previous arachnoiditis. There was no evidence of active infection. Over the next few days her neurological state deteriorated further. Her subsequent course was complicated by metabolic disorders and infections. Her clinical condition continued to deteriorate and she died on the 72nd hospital day.

Necropsy

Necropsy confirmed the diagnosis of idiopathic pulmonary haemosiderosis with accompanying mild left ventricular cardiac hypertrophy. The external surfaces of the 1350g brain, brainstem, cerebellum and cerebral vasculature appeared normal for age, however, focal softening and grey discoloura-

tion were identified in the optic chiasm. Horizontal sectioning of the brain revealed periventricular softening in the white matter surrounding the anterior horns of both lateral ventricles with extension to the medial head of both caudate nuclei. A 1.0 cm grey, softened lesion was also discovered medial to the posterior genu of the left internal capsule and surrounding the posterior horns of both lateral ventricles. The external and horizontally sectioned surfaces of the cerebellum appeared normal.

Horizontal sections of the pons revealed a 6.0 mm diameter tan-grey lesion subjacent to the cerebral aqueduct extending from the upper pons to the pontomedullary junction. Lesions were not found in the medulla. However, sections of the cervical, thoracic, lumbar, and sacral spinal cord also showed multiple areas of focal softening and grey-tan discolouration of the posterior and lateral funiculi.

All sections were evaluated using Masson's, Feigin and Luxol fast blue-periodic acid Schiff (LFB-PAS) stains. Additional sections of the optic chiasm, pons and spinal cord were evaluated using the peroxidase-anti-peroxi-

dase technique and a polyclonal antibody recognising myelin basic protein³ (DAKO Corporation, Santa Barbara, CA). The sections of optic nerves and chiasm revealed multiple zones of demyelination associated with a reduction in oligodendrocytes (fig D). These areas were infiltrated by lipid laden macrophages and small lymphocytes which cuffed intact, patent blood vessels. Feigin stains showed relative preservation of axons in the optic nerves. In contrast, sections of the genu of the corpus callosum showed complete preservation of myelin. Cortical grey and sub-cortical white matter from the frontal and parietal lobes was histologically normal. Zones of extensive demyelination, oligodendrocyte loss and focal necrosis infiltrated by lipid-laden macrophages accompanied by a moderate perivascular lymphocytic infiltrate and reactive astrocytosis was seen in multiple sections adjacent to the anterior and posterior horns of both lateral ventricles. The cerebellum was histologically normal.

The rostral mesencephalon was histologically normal. However, sections of the rostral pons revealed a periventricular zone with loss of myelin extending through the right superior cerebellar peduncle to the right locus coeruleus (fig B and C). Large numbers of lipid laden macrophages and occasional lymphocytes populated this lesion. Lymphocyte-cuffed blood vessels within and near the lesion were neither necrotic nor thrombosed. Subependymal protoplasmic astrocytes lined the margins of this lesion. The subjacent locus coeruleus was entirely intact. Sections through the mid-pons revealed ventromedial extension of the lesion into the nucleus of the median eminence which showed neuronal sparing despite severe loss of myelin and an extensive mononuclear infiltrate. Feigin stains revealed a mild axonal loss within the lesion. The medulla was normal.

The cervical spinal cord showed moderate axon-sparing demyelination with a reduction in oligodendrocytes in the posterior and lateral funiculi. These areas contained moderate lipid-laden macrophagic and lymphocytic infiltrate. Lymphocytes and occasional neutrophils also cuffed many intact, patent blood vessels. A chronic inflammatory infiltrate permeated the dorsal horns and replaced the ventral horns where moderate necrosis and neuronal loss were evident. The anterior funiculi appeared relatively preserved within the cervical cord although the ventral nerve roots showed moderate demyelination and axonal swelling. The thoracic spinal cord also exhibited striking demyelination, axonal preservation, an extensive macrophagic infiltrate and mixed acute and chronic perivascular infiltrate in the posterior and lateral funiculi. However, the anterior funiculus, Clarke's nucleus and neurons of the ventral horns thoracic segments, were relatively spared. Sections of lumbar segments revealed lesions similar to that in the cervical cord. Sections of the sacral segments exhibited only mild demyelination and infiltration of macrophages. There was no evidence of vasculitis or

thrombosis in any section. Demyelination was neither perivascular nor accompanied by concentric areas of remyelination.

Discussion

The distribution and histopathological pattern of central nervous system lesions in our patient are characteristic of multiple sclerosis (MS). These included extensive demyelination of the optic nerves, numerous periventricular plaques, extensive spinal cord demyelination, and demyelination with variable axonal sparing and chronic perivascular inflammatory infiltrates. However, features such as the abrupt, lethal, monophasic course and severity of lesions in our patient are unique to acute fulminant MS of the Marburg type. The presence of similarly-aged acute plaques with extensive macrophagic infiltrate, variable axonal loss and necrosis identified in our patient also resemble the pathological changes originally described by Marburg.²

Descriptions of cases verified at necropsy suggest that acute MS of the Marburg type is a fulminant, fatal variant which causes death by destruction of vital brainstem structures. Harper described a fatal two week course of acute MS producing periventricular plaques in the pons and basal ganglia of a 48 year old woman.⁴ Guillain and Alajouanine described rapid onset of bulbar symptoms, neurological deterioration and death within three weeks in a patient with acute pontine and medullary plaques.⁵ Death after four weeks with prominent brainstem involvement was also reported by Banerjee *et al*,⁶ and Mendez and Pogacar.⁷ This common feature of brainstem involvement may also occur in patients with a longer clinical course, as in our patient and that of Lassmann *et al*, where the patient's ultimate demise after a 12 week illness, appeared to coincide with clinical and necropsy evidence of brainstem involvement.⁸

Somatic lesions have not been associated with MS although a higher incidence of malignancy has been suggested.⁹ We believe the concomitant affliction with acute MS and idiopathic pulmonary haemosiderosis is coincidental.

The protracted course in our patient compared to previously reported patients is of interest because of its potential relationship to concomitant steroid therapy. Glucocorticoid therapy for idiopathic pulmonary haemosiderosis in our case may have contributed to the 12 week survival after onset of symptoms which contrasts with the two to four week survival characteristic of acute MS.⁴⁻⁷ The corticosteroids may also have reduced the perivascular lymphocytic infiltrate in some lesions. A similar attenuation of perivascular infiltrates has been described in a patient dying with acute MS while treated with methylprednisone.¹⁰

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