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CASE REPORT

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Central pontine myelinolysis in AIDS

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Abstract Central pontine myelinolysis (CPM) is an uncommon complication in sick patients with severe underlying disorders such as chronic alcoholism, malignancy, malnutrition and hyponatraemia. We report two patients with advanced HIV infection who developed CPM. In one case the diagnosis was not suspected in life, in the other the diagnosis was made just before death, on the basis of magnetic resonance (MR) imaging appearances. At post mortem there was a close correlation between the MR abnormalities and the anatomic changes in the pons.

Key words Central pontine myelinolysis · AIDS · Magnetic resonance imaging · Autopsy

Introduction

Central pontine myelinolysis (CPM) was first described in 1959 in four patients, three of whom were alcoholic and one was severely malnourished [1]. Autopsy revealed a single sharply outlined focus of myelin destruction in the rostral part of the pons, involving all fibre tracts but largely sparing nerve cells and axis cylinders. Subsequently, there have been many reports of CPM, the majority in adults, and invariably associated with severe underlying disorders including chronic alcoholism, chronic renal failure treated with dialysis, hepatic failure, advanced lymphoma, carcinoma, cachexia and malnutrition from a variety of causes, severe bacterial infections, dehydration, burns and hyponatraemia (and its rapid correction) [5, 7, 13, 14].

The clinical presentation varies between rapidly evolving spastic paraparesis with pseudobulbar palsy, and changes in mental state with confusion or coma. Some cases are clinically 'silent' and are only discovered at autopsy. CPM has been described in patients with acquired immunodeficiency syndrome (AIDS) [2, 4, 6, 8, 11]; in all cases the diagnosis was made at autopsy. In this report we describe CPM occurring in two patients with advanced HIV infection. In one the diagnosis was made prior to death, on the basis of magnetic resonance (MR) imaging appearances, in the other the diagnosis was not suspected in life.

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Case reports

Case 1

Patient 1 was a 36-year-old HIV-1 antibody-positive white homosexual man who presented with a 1-week history of lethargy, fever and intermittent disorientation. He was receiving chemotherapy with liposomal doxorubicin for cutaneous and pulmonary Kaposi's sarcoma and antiretroviral therapy with stavudine, lamivudine and indinavir. On admission, general examination revealed extensive cutaneous Kaposi's sarcoma. The cranial nerves and limbs, and sensory examination of all modalities were normal. A full blood count revealed a normochromic anaemia, haemoglobin (Hb) 12.8 g/100 ml, a normal white blood count and thrombocytopenia, platelets 73×10^9/l. A $CD4^+$ lymphocyte count was 70×10^6/l (normal range 350×10^6–2200×10^6/l). Urea, electrolytes, calcium, phosphate and liver function tests were all normal save for a serum albumin of 22 g/l (normal 35–53 g/l). Blood cultures were negative. At lumbar puncture the CSF protein was slightly elevated at 58 mg/100 ml, with no cells, stain and culture negative, syphilis and toxoplasma serology negative. DNA amplification, by the polymerase chain reaction, for herpesviruses 1 and 2, cytomegalovirus, varicella zoster virus, Epstein Barr virus and JC virus was all negative.

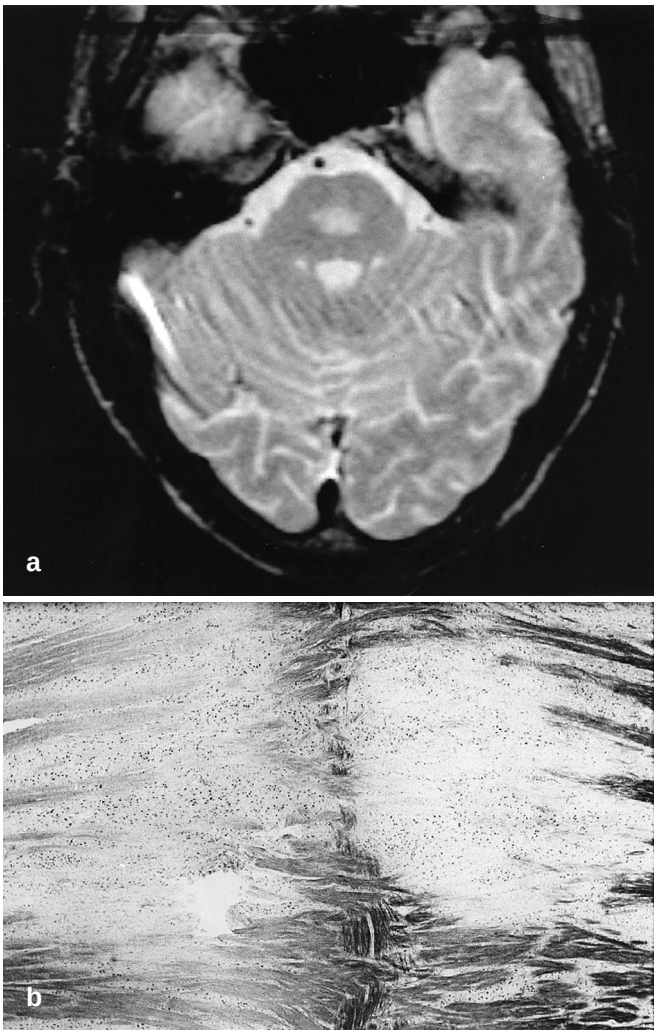

Fig. 1 **a** Case 1. Transverse T2-weighted magnetic resonance image through the pons showing a well-defined oval shaped high signal lesion centrally within the pons. There is no mass effect nor surrounding oedema. **b** Photomicrograph of the basis pontis in case 1 showing a well-circumscribed and completely demyelinated area on the *right* of the mid-line and, on the *left*, a symmetrically located area, in which myelin is still partially present. Note that the pontine neurons within both areas are still recognisable. Luxol fast blue/cresyl violet. **b** × 270

Over the 20 days following admission, the patient was increasingly anorexic. Total parenteral nutrition (TPN) was commenced (sodium content 80 mmol/day). After 3 days of TPN the serum sodium fell from 134 mmol/l to 126 mmol/l. At this time the patient was drowsy and variably confused. Examination revealed normal cranial nerves and full power and sensation in the limbs. The following day the serum sodium level had risen to 132 mmol/l – an increase of 6 mmol in 24 h. On day 26 after admission an MRI scan of the head revealed within the central pons a focus of increased signal on T2-weighted images (Fig. 1a). The lesion did not extend up into the midbrain or down into the medulla oblongata. Terminally, the patient became neutropenic and septic; he died on day 39. The serum sodium had remained between 134 mmol/l and 143 mmol/l and the serum albumin ≤ 21 g/l throughout.

At autopsy the cause of death was pulmonary and cutaneous Kaposi's sarcoma, CMV pneumonia and lymphoplasmacytoid B cell lymphoma in the liver. Neuropathology showed the fixed brain weight was 1440 g and was symmetrical and of normal size. On cut section, the only macroscopic abnormality was the presence of areas of discolouration in the right pontine tegmentum and in the right basis, partly occupying the region of the cortico-spinal tracts. On histological examination the pons showed a central area of demyelination, extending bilaterally to involve the transverse fibres of the basis, (Fig. 1b) with an associated prominent infiltrate of foamy macrophages (Fig. 2). Neuronal cell bodies within the pontine nuclei were well preserved and there was relative axonal preservation within the lesion, although silver impregnation showed some axonal damage with axon retraction balls. Furthermore, immunohistochemical staining for β-amyloid precursor protein (β-APP) revealed considerable and extensive axonal damage, which extended also outside the basis pontis affecting the medial lemniscus. Elsewhere in the pons there were small areas in which axons expressed β-APP. These were scattered in the superior cerebellar peduncles and in both transverse and descending tracts of the basis pontis. Small foci of macrophages and activated microglia were also seen with a similar distribution. In the latter areas neither demyelination nor retraction balls were seen. The remainder of the neuropathological examination was normal.

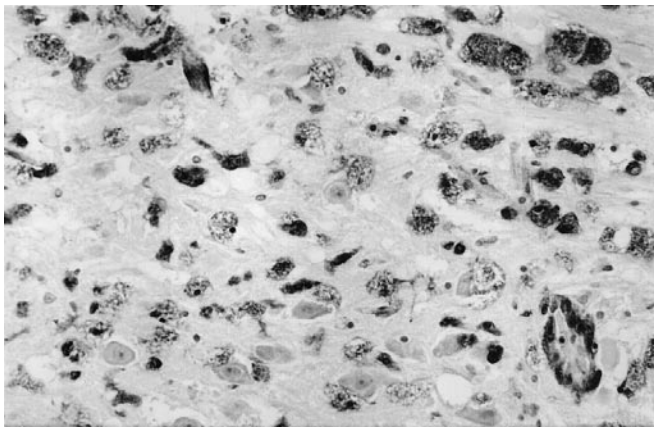

Fig. 2 The demyelinated areas contain large numbers of foamy macrophages. These can be emphasised by staining with the lectin RCA-120, which visualises cells of microglia/macrophage lineage. × 270

Case 2

Patient 2 was a 35-year-old HIV-1 antibody-positive white homosexual man who presented with fever, dyspnoea, poor appetite and weight loss. He had begun cyclic chemotherapy with vincristine and bleomycin as treatment for extensive cutaneous Kaposi's sarcoma 4 months before admission. He had consumed > 60 units of alcohol per week for many years. On general examination the patient looked thin; there was extensive cutaneous Kaposi's sarcoma. Neurological examination was unremarkable. Investigations showed that the serum sodium 126 mmol/l, potassium 2.1 mmol/l and serum albumin 22 g/l. There was a pancytopenia; Hb 9.3 g/100 ml, WBC 0.6×10^9/l and platelets 95×10^9/l. At fibre-optic bronchoscopy extensive Kaposi's sarcoma was noted: culture of bronchoalveolar lavage fluid grew *Staphylococcus aureus*. Despite parenteral antibiotics the patient deteriorated steadily, becoming intermittently confused, and died on day 26 of hospitalisation. Examination the day before death revealed only cachexia and global weakness (MRC grade 4/5). He had remained mildly hyponatraemic throughout the admission (serum sodium 132–135 mmol/l). The maximum increase in sodium was 4 mmol/24 h. In addition the serum albumin never rose above 21 g/l.

At autopsy the cause of death was renal and pulmonary failure, and visceral Kaposi's sarcoma. Neuropathology showed the fixed brain weighed 1520 g and was of normal size and shape: the leptomeninges were opaque. The structures at the base appeared normal. Coronal sections did not show obvious abnormalities except

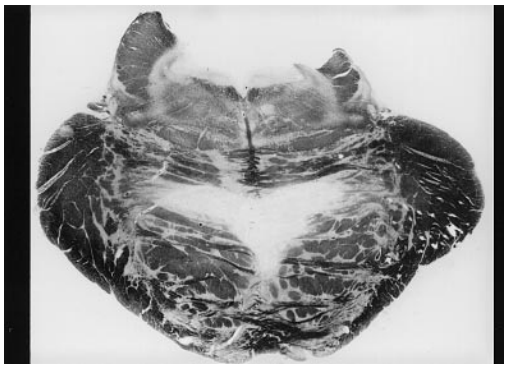

Fig. 3 The basis pontis in case 2 included a large triangular area of complete myelin loss, extending symmetrically across the mid-line. Luxol fast blue

for a small and well-circumscribed nodule with necrotic centre, situated in the left caudate nucleus. Histological examination revealed B cell lymphoma localised to the deep grey nuclei; HIV-1 encephalitis; multiple microabscesses localised in both grey and white matter in the parietal lobes and cerebellar hemispheres containing Gram-positive organisms and a large cystic area in the mid-line of the basis pontis (Fig. 3). The area was roughly triangular with its base dorsally situated and measuring 20 mm. The edges of the cyst were relatively clear cut. It showed complete myelin loss and contained large amounts of foamy macrophages and many, relatively well-preserved, nerve cells. No inflammatory cells were seen.

Discussion

Both of these patients had advanced HIV disease, were anorexic, hypoalbuminaemic and were receiving systemic chemotherapy for disseminated Kaposi's sarcoma. In addition, one had a chronic heavy alcohol consumption. At autopsy both were found to have a lymphoma. Both our patients were variably hyponatraemic over many days. Previous reports of CPM are strongly associated both with hyponatraemia per se and particularly with its very rapid correction [7, 12]. It is recommended that the serum sodium is restored by less than 10 mmol/l in the first 24 h [7, 12]. In neither of our patients did the serum sodium rise by more than 6 mmol/l in 24 h.

CPM has previously been reported at autopsy in patients with AIDS [2, 4, 6, 8, 11]. One case, a woman with advanced HIV infection, presented 1 month before death with fevers, *P. carinii* pneumonia, thrombocytopenia, hypocalcaemia and hyponatraemia. At 2 weeks before death she became agitated and confused. Autopsy revealed CPM and disseminated (including cerebral) toxoplasmosis and cytomegalovirus infections [11]. In a second case, the clinical presentation was not specified; however, the patient was hyponatraemic, between 130 and 132 mmol/l, for 1 month before death [2]. In a third case, a man with advanced HIV infection presented with malaise, anorexia and fever and a right VI nerve palsy, ptosis and dysarthria. Investigations revealed mild anaemia, hypoalbuminaemia (albumin 19 g/l) and a lymphomatous pleural effusion; a computed tomography scan of the head was normal. At autopsy there was disseminated lymphoma including stomach and meninges. In the brain the only abnormality was CPM [6]. In none of these cases was the diagnosis suspected in life and in only one was neuro-imaging performed ante mortem. While in the first two cases hyponatraemia was present for some time before death, in the third the serum sodium was normal but the patient was hypoalbuminaemic and, thus, was similar to our cases.

A histologically similar lesion to CPM has been described in patients with HIV infection and labelled focal pontine leukoencephalopathy [15]. This consists of several well-demarcated areas of vacuolation involving the ponto-cerebellar tracts with loss of myelin accompanied by calcification and necrosis of axons. In addition there is no particular predilection for the central area of the pons [15]. The condition was originally described in patients without HIV infection who had received chemotherapy or radiotherapy to the central nervous system [3].

In keeping with the majority of patients with CPM, our patients had no focal neurological deficits which could be ascribed to the pontine lesion, although at autopsy the focus impinged on the cortico-spinal tracts in case 1; their episodes of confusion were attributed to intercurrent sepsis. This reflects the fact that the lesion in CPM is small often extending only 3 or 4 mm either side of the mid-line within the centre of the pons and involves only a small number of ponto-cerebellar or cortico-pontine fibres. Consequently MR imaging may not identify any pontine abnormality [10]. In contrast in our patient the MR imaging appearances in life were of a well-defined oval area of high signal, on T2-weighted images, within the central area of the pons. This closely corresponded to the anatomic lesion seen at autopsy. In a previous study of CPM in 13 patients without HIV infection, the diagnosis was made clinically in 5 patients and at autopsy in 8. Of the 13 patients, 11 had MR imaging studies, in life in the 5 with a clinical diagnosis and in 6 of the 8 with an autopsy diagnosis the MR imaging was performed on fixed sections of brain stem. The interval between autopsy/tissue fixation and imaging ranged from 1 to 16 years (mean 8 years) [9]. In this study there was a close correlation between the post-mortem MR imaging abnormalities and the autopsy appearances [9].

In conclusion, CPM may occur in patients with AIDS. Several factors may be associated, including advanced HIV infection, disseminated malignancy and the treatment thereof with systemic chemotherapy, anorexia, chronic alcoholism, prolonged hyponatraemia and hypoalbuminaemia. Like critical illness neuropathy it probably results from interaction of several factors, although hyponatraemia is the most obvious. Abnormalities within the pons seen on MR imaging correspond closely to autopsy findings. With more general availability of MR imaging this pathological process may increasingly be recognised as a cause of deterioration in the sick patient with metabolic derangement.

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