Combined HIV-CMV encephalitis presenting with brainstem signs

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SUMMARY Two cases of combined HIV-CMV encephalitis are described. One presented with a sixth nerve palsy and a tetraparesis, the other with an internuclear ophthalmoplegia. Pathologically brain stem involvement was predominantly due to CMV.

Brainstem encephalitis is a term coined by Bickerstaff to describe eight cases1 of encephalitis with predominant brainstem signs, seven transient, one fatal, following a mild viral illness in immunocompetent patients. No aetiological agent was found. Subsequently Herpes simplex has been demonstrated serologically2-4 and pathologically5-6 as a cause of "brainstem encephalitis". Brainstem signs have also been described in Herpes zoster encephalitis.7 Focal signs have been reported with adenovirus8 and ECHO 25 encephalitis in the immunocompetent, though not involving the brainstem. Prominent brainstem signs have also been described in paraneoplastic encephalomyelitis.9 We describe combined human immunodeficiency virus—cytomegalovirus (HIV-CMV) encephalitis presenting with brainstem signs in two patients with the acquired immunodeficiency syndrome (AIDS) and review previously reported cases of AIDS with brain stem signs and pathological evidence of viral encephalitis.

Methods and case reports

Neuropathology The brains were fixed for three weeks in 10% buffered formalin. At least 15 blocks were taken from the cerebral hemispheres, brainstem, deep grey nuclei and cerebellum and processed to paraffin wax. Sections were stained with haematoxylin and eosin, haematoxylin-van Gieson, Luxol fast blue/cresyl violet, Gleece-Marsland silver impregnation. The following antigens were looked for using immunoperoxidase staining with a modified avidin-biotin method and the following antisera: cytomegalovirus (CMV, DaKo) and glial fibrillary acidic protein (GFAP, DaKo).

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Case 1. Internuclear ophthalmoplegia was the presentation of the acquired immunodeficiency syndrome two years after HIV seropositivity was diagnosed

A 34 year old male company director was found to be HIV antibody positive in July 1985. Both his wife, an IV drug abuser, and his daughter aged 4 were HIV antibody positive. He had been treated with acyclovir 200 mg 5/day for herpes genitalis and with ketoconazole and amphotericin lozenges for oral candida. In August 1986 he had fever, headache and a sore throat with an ulcer on the left tonsil. A beta haemolytic streptococcus was isolated from the throat and he responded to penicillin. Axillary and inguinal lymphadenopathy was noted. In January 1987 he complained of malaise, weight loss and transient loss of vision in the left eye twice. His visual acuities were 6/9 bilaterally. He had cotton wool spots in both retinae. Neurological examination was normal. CT showed slight generalised atrophy. In February 1987 an HIV antigen test (ELISA) was positive in blood and neutralisation showed 90 units/ml. In March 1987 he was treated for Staphylococcus aureus conjunctivitis. In April 1987 zidovudine 100 mg qds was started.

He was admitted to hospital on 22 July 1987 with a 7 day history of horizontal diplopia and numbness in the left arm. He had daily frontal headaches, minor impairment of short term memory and some intermittent diarrhoea for two months. He appeared a little vague but was fully alert and orientated. He had bilateral internuclear ophthalmoplegia and lateral gaze palsy with 70% abduction and 80% abduction of both eyes, preserved convergence, bilateral ataxic horizontal, and up gaze vertical, nystagmus. Papillary reactions were normal. There were no long tract signs. General examination was unremarkable. A magnetic resonance brain scan was normal. The cerebrospinal fluid showed 1 lymphocyte, total protein 0-8 g/l, albumin 0-6 g/l (normal <0-4), IgG 0-2 g/l (normal <0-004). Auditory brain stem evoked responses were normal. Haemoglobin 10-6 g/l, RBC 3-23 × 1012/l, MCV 95-5 fl, MCH 32-8 pg, platelets 335 × 109/l, WBC 1-7 × 109/l, lymphocytes 17%, neutrophils 76%, monocytes 6%, eosinophils 1%. Urea and electrolytes, liver function tests, serum calcium and phosphate and plasma proteins were normal.

Shortly after he developed upgaze paresis (fig 1) and then
Fig 1  Internuclear ophthalmoplegia (case 1). Top left: normal downgaze. Top right: paresis of upgaze. Bottom right: looking to the right. Bottom left: looking to the left.

Fig 2  Photomicrograph from case 1 showing a cluster of multinucleated giant cells. The largest in the centre of the picture contains haphazardly distributed nuclei. (H&E x 300.)

Fig 3  A glial nodule adjacent to a blood vessel in the brainstem of case 1. Cells are loosely arranged and some have a rod shaped nucleus. (H&E x 300.)

Fig 4  Numerous astrocytes in the periventricular regions in case 1 have large intranuclear inclusions typical of CMV. (H&E x 300.)

Fig 5  Low power photomicrograph of the pons of case 2, showing a large poorly demarcated area of myelin loss on the right side. Luxol fast blue/Nissl.
confusion and marked short term memory impairment. A mini mental state examination was 24/30 two weeks after admission. Trunkal ataxia and an almost total bilateral internuclear and lateral gaze palsy. In addition, drug paresis (30%) and nystagmus were noted. Bilateral facial weakness ensued. A 7 day course of methylprednisolone was followed by some modest improvement in the ophthalmoplegia and he appeared less drowsy. The subsequent course was punctuated by an episode of dehydration, drowsiness, fluctuating confusion, motor agitation, and poor recent memory. Delirium and confabulation became prominent. He often thought that staff he had not seen before were old acquaintances and believed there were hyenas and wolves in the ward, but true hallucinations were not a feature. He had one generalised seizure. By the 29 August his MMS score was 17/30 and a week later 11/30. An EEG on 1.9.87 showed bilateral delta waves of maximal amplitude anteriorly. He developed bronchopneumonia and died on 7 September 1987.

Pathological findings
The brain weighed 1395 g and on cut section did not show any abnormalities except slightly dilated lateral ventricles. Histological examination showed three main types of pathology: (a) HIV encephalitis was present in the cerebral hemispheric white matter and consisted of variable numbers of multinucleated giant cells (MGC). These were found in isolation or in small groups and varied in size from round to oval or irregularly polygonal. They had eosinophilic cytoplasm and variable numbers of round nuclei (fig 2). In the cerebellum, the white matter was slightly oedematous, there was a moderate increase in the number of cells but no MGC were seen.
(b) microglial nodules were present throughout the whole brain stem. They were relatively small and consisted of round or elongated cells. An occasional astrocyte was also included but no inclusion bodies could be seen. In the brainstem (fig 3) a few nodules were seen in the inferior olives, basis pontis and in the tegmentum of the midbrain. No multinucleated giant cells were seen in the brainstem.
(c) diffuse necrotising ventriculo-encephalitis was found, consisting of a disappearance of ependymal lining, subpial necrosis and presence of macrophages and large astrocytes. Many of the latter contained round or cigar shaped inclusions (fig 4). This process involved the whole aqueduct and floor of the fourth ventricle with almost complete disappearance of the nuclei of the tenth and twelfth cranial nerves on both sides and of one dorsal cochlear nucleus. The process impinged on the medial longitudinal fasciculus. In the pons both loci coerulei were severely damaged. Immunocytochemical methods using CMV antibodies confirmed the presence of cytomegalovirus within the nuclei of the astrocytes.

Case 2. A patient with AIDS developed a right VI nerve palsy and tetraparesis and later confusion and drowsiness.
A 37 year old male homosexual with one previous gonorrheal infection had Pneumocystis carinii pneumonia in August 1985 when he was found to be HIV antibody positive. In November 1985 he had diarrhoea, tiredness and night sweats. In December 1985 Mycobacterium avium intracellulare was isolated from blood. In March 1986 he was noted to have a periareal Herpes simplex ulcer. On 10 April 1986 he was admitted with fever, vomiting, diarrhoea, cough and headache for 4 days. He had a temperature of 40°C. Antituberculous therapy was started when typical Mycobacterium tuberculosis were isolated from blood, bone marrow and stools. Cerebrospinal fluid examination showed no cells, glucose 2.8 mmol/l (blood 4.0), protein 0.16 g/l and CSF cultures were negative. He was anaemic: haemoglobin 8.6 g/dl. MCV 87.4 fl, MCH 29.4 pg, platelets 110 x 10^9/l, WBC 4.1 x 10^9/l (lymphocytes 24-1%, monocytes 3.7%, neutrophils 72.2%). Faecal occult blood was positive. The following were normal or negative: Barium enema, toxaemia titre, VDRL, TPHA, hepatitis B. For the next two days he appeared slower in responding to questions, stared and smiled. This was followed by a heightened affect appearing more lively than before. A friend stated that he had reacted to stress in this way in the past. Formal psychiatric examination a day later found no evidence of organic brain disease. On 20 April he had a generalised seizure. CT showed mild generalised atrophy. He was well on discharge on 3 June 1986.
On 3 August 1986 he was readmitted to hospital with a 3 week history of malaise, vomiting and horizontal diplopia and progressive weakness of the left limbs for 2 weeks. He was alert and cooperative and had a complete right VI nerve palsy, exaggerated jaw jerk, a mild tetraparesis, predominantly left sided, with left extensor plantar response and impaired pin prick and temperature sensation on the left with an upper limit at T2. CT showed minor generalised atrophy as before, but no focal lesions. He became confused and progressively drowsy and died on 26 August 1986.

Pathological findings
The brain weighed 1460 g and was normal in shape and size. Coronal sections showed symmetrically dilated ventricles. The cortex, white matter and deep grey nuclei were macroscopically normal. The white matter of some gyri of the inferior surface of the left cerebellar hemisphere, a large area in the medio-lateral cerebellar hemisphere and a large area in the medio-lateral (right) pons showed grey discoloration (fig 5).

Histological examination showed various types of lesions involving both grey and white matter. Diffuse necrotising ventriculo-encephalitis similar to that seen in case 1 was seen. Microglial nodules were seen predominantly in the cortical grey matter and were composed of aggregates of macrophages, rod cells and, on occasion, included a large astrocyte bearing an intranuclear inclusion. Foci of parenchymal necrosis consisted of foamy macrophages, some perivascular inflammatory infiltrates, swollen or fragmented axons and astrocytes with intranuclear inclusions. In both the cerebellum and pons the areas of necrosis included a few multinucleated giant cells (MGC) typical of HIV infection. Immunocytochemical methods using GFAP and CMV antibodies confirmed the astrocytic nature of the cells containing the intranuclear inclusion and the presence of the cytomegalovirus.

Discussion
We have described two patients who presented with brainstem signs and had pathologically demonstrated combined HIV-CMV diffuse encephalitis. In case 1...
Table: Brainstem encephalitis in patients with AIDS

<table>
<thead>
<tr>
<th>Author</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Aetiology</th>
<th>Brainstem signs</th>
<th>CSF</th>
<th>Radiology</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horoupian et al</td>
<td>35M</td>
<td>M</td>
<td>Adenovirus 31</td>
<td>Tetraparesis upgaze palsy pseudobulbar palsy</td>
<td>WBC 1</td>
<td>CT: bilateral ganglia calcifications</td>
<td>CSF: Adenovirus 31 cultured PM: bilateral degeneration of corticospinal and pontine fibers in pons, Gial nodule in brainstem</td>
</tr>
<tr>
<td>Behar et al</td>
<td>33M</td>
<td>M</td>
<td>CMV L VI</td>
<td>Horizontal &amp; vertical Nystagmus</td>
<td>99 WBC (57% PMN, 33% L, 10% M) P: 1.04 g/l G: 2.1 mmol/l</td>
<td>CT: normal</td>
<td>Multiple petechial hemorrhages around 3rd &amp; 4th ventricles subependymal</td>
</tr>
<tr>
<td>Laskin et al</td>
<td>46M</td>
<td>M</td>
<td>CMV/HSV</td>
<td>Bilateral ptosis, dysconjugate gaze</td>
<td>9 WBC (5 PMN, 4 L) P: 5.24 g/l G: 1.9 mmol/l</td>
<td>CT unenhancing lesions R cerebellopontine angle</td>
<td>Disseminated organizing toxoplasma abscesses in brainstem and hemispheres</td>
</tr>
<tr>
<td>Masdeu et al</td>
<td>43M</td>
<td>M</td>
<td>CMV</td>
<td>L hemiparesis R VI R gaze palsy L VII L facial anaesthesia</td>
<td>0 WBC P: 0.21 g/l G: 3.2 mmol/l</td>
<td>CT: R internal capsule lesion MRI: lesion R internal capsule, L upper pons</td>
<td>R internal capsule biopsy; CMV on EM, immunohistochem</td>
</tr>
<tr>
<td>Jacobson et al</td>
<td>42M</td>
<td>M</td>
<td>CMV</td>
<td>Dysconjugate gaze nystagmus</td>
<td>1550 WBC P: 1.78 G: 1.56 mmol/l</td>
<td>CT: diffuse atrophy, low density lesions posterior fossa</td>
<td>Necrotising encephalomyelitis with CMV inclusions particularly in pons and medulla</td>
</tr>
<tr>
<td>Fuller et al</td>
<td>34M</td>
<td>M</td>
<td>CMV/HIV</td>
<td>Internuclear ophthalmoplegia bilateral VII</td>
<td>1 WBC P: 0.5 g/l</td>
<td>CT: slight atrophy MRI: normal</td>
<td>Microglial nodules in brainstem multinucleated giant cells in hemispheres and brainstem</td>
</tr>
<tr>
<td></td>
<td>37M</td>
<td>M</td>
<td>CMV/HIV</td>
<td>Tetraparesis</td>
<td>0 WBC P: 0.16 g/l G: 2.8 mmol/l</td>
<td>CT: atrophy</td>
<td>Pontine demyelination multinucleated giant cells and CMV inclusions in brainstem and hemispheres</td>
</tr>
</tbody>
</table>

*Toxoplasmosis was the probable cause of the brainstem signs in this patient.

Pathological findings in the pons consisted of involvement of the periventricular structures by CMV encephalitis and of scattered microglial nodules. The latter finding is non specific and can be explained in encephalitic processes of viral and non-viral origin. The deterioration in higher cerebral function, delusions and generalised seizures may be explained by the diffuse giant cell encephalopathy with a CMV perivenricticulitis. In the second case the first episode of altered cerebral function followed some days later by a seizure was transient and associated with systemic illness. The development of the right VI nerve palsies and tetraparesis three months later are consistent with the pontine lesions, which were judged predominantly due to CMV encephalitis pathologically. The gradual deterioration in higher function seems associated with the diffuse encephalopathy with predominant CMV involvement on histological grounds.

*Herpes simplex, Herpes zoster and measles encephalitis have been described in immunosuppression associated with lymphoma and chemotherapy. In this group one case had brainstem signs (vertical nystagmus and appendicular ataxia) though no cause was found. CMV encephalitis is rare in the immuno-compotent and brainstem signs have not been reported in this group or in the immunocompromised. In patients with AIDS CMV encephalitis is common, occurring in 17% and 26% in pathological series. The microglial nodules occur most frequently in the brainstem but are not specific. CMV encephalitis is not definitively diagnosed clinically, radiologically or serologically but on biopsy or at postmortem though CMV has been isolated in CSF. Brainstem signs in patients with HIV encephalitis alone have not been described although ataxia has been reported. The table summarises pathologically confirmed viral encephalitis in patients with AIDS with recorded brainstem signs. The table excludes cases where brainstem signs are described without pathological confirmation of aetiology and where pathological findings are without clinical correlates. In all these cases there was an associated diffuse viral encephalitis. Two of these cases also presented with brainstem signs. The differential diagnosis of an HIV positive patient presenting with brainstem signs includes toxoplasmosis and primary brain lymphoma. Ataxia and dysarthria have been described in progressive multifocal leukoencephalopathy. Pathology found in
immunocompetent patients such as multiple sclerosis and vascular events should also be considered. Systemic lymphoma can produce cranial polyneuropathies which are often the initial presentation. CMV is a cause of brainstem signs in patients with AIDS with encephalitis (table). It remains possible that HIV encephalopathy may present with brain stem signs; our case 2 had multinucleated giant cells in the brainstem but our case 1 did not provide pathological evidence since they were not found in the pons. As it is difficult to make a diagnosis of CMV encephalitis in life anti CMV chemotherapy should be considered in AIDS patients presenting with brainstem signs.

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References