

4. Grignani G, Gobbi PG, Piccolo G, Bertoloni D, Rossi A, Pieresca C, Legnani MC, Ascari E (1992) Progressive necrotic myelopathy as a paraneoplastic syndrome: report of a case and some pathogenetic considerations. *J Intern Med* 231: 81–85
5. Hughes M, Ahern V, Kefford R, Boyages J (1992) Paraneoplastic myelopathy at diagnosis in a patient with pathological stage IA Hodgkin disease. *Cancer* 70: 1598–1600
6. Inwards DJ, Piepgras DG, Lie T, O'Neill BP, Scheithauer BW, Habermann TM (1991) Granulomatous angitis of the spinal cord associated with Hodgkin's disease. *Cancer* 68: 1318–1322
7. Kuroda Y, Miyahara M, Sakemi T, Matsui M, Ryu T, Yamaguchi M, Sasadomi E, Sugihara H (1993) Autopsy report of acute necrotizing opticomyelopathy associated with thyroid cancer. *J Neurol Sci* 120: 29–32
8. Lester EP, Feld E, Kinzie JJ, Wollmann R (1979) Necrotizing myelopathy complicating Hodgkin's disease. *Arch Neurol* 36: 583–585
9. Mancall EL, Rosales RK (1964) Necrotizing myelopathy associated with visceral carcinoma. *Brain* 87: 639–656
10. Ojeda VJ (1984) Necrotizing myelopathy associated with malignancy. A clinicopathologic study of two cases and literature review. *Cancer* 53: 1115–1123
11. Peress NS, Su PC, Turner I (1979) Combined myelopathy and radiculoneuropathy with malignant lymphoproliferative disease. *Arch Neurol* 36: 311–313
12. Richter RB, Moore RY (1968) Noninvasive central nervous system disease associated with lymphoid tumors. *Johns Hopkins Med J* 122: 271–283
13. Whiteley AM, Hauw JJ, Escourolle R (1979) A pathological survey of 41 cases of acute intrinsic spinal cord disease. *J Neurol Sci* 42: 229–242

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Fatal brain stem encephalitis due to herpes simplex virus type 1 in AIDS

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Sirs: Despite the increasing incidence of herpes simplex virus (HSV) systemic infection in HIV-infected persons, HSV-1 infection of the central nervous system (CNS) is very rare in this population [1–3]. The manifestations and course of HSV encephalitis (HSVE) in HIV-infected patients are much more variable than in immunocompetent hosts. Classical limbic encephalitis is rare [1, 3], while diffuse chronic encephalitis with a more indolent course is frequent [4]. HSV-1 infection of the brain stem has only been described once, in a patient with AIDS [2]. We report a case of HSV-1 brain stem encephalitis revealed by bilateral trochlear (fourth) nerve palsy followed by left hemiplegia that was unusual because of the absence of past or recent herpes cutaneous eruption. The necrotic and haemorrhagic encephalitis was mainly localized to the brain stem.

A 38-year-old woman infected by HIV-1 through blood transfusion in 1984 (CDC stage III) presented with a vertical diplopia. A bilateral fourth nerve palsy was the only clinical finding. In particular, there were no skin lesions suggestive of HSV infection. MRI of the brain and cerebrospinal fluid were normal at the time, and polymerase chain reaction (PCR) testing [5] for HSV and cytomegalovirus (CMV), and stains and culture for viruses, fungi and bacteria, were negative. The CD4+

cell count was 24/mm³ (1% of total lymphocytes). The diplopia persisted unchanged for 3 months, when a left sensorimotor hemiparesis progressively appeared with fever (39°C). MRI of the head showed a bicingular enhanced lesion, with no mass effect but no lesion in the midbrain tegmentum (Fig. 1). The electroencephalogram was normal. Antitoxoplasmic therapy had no effect. Her neurological condition worsened to left hemiplegia but her mental status remained normal throughout. Repeated brain MRI only showed the same bicingular hyposignal lesion in the T1-weighted sequences, still enhanced after gadolinium infusion, without any change. CSF examination was not repeated. Three months after onset she suddenly fell into a coma and died within a few hours. Autopsy was limited to the brain. Blocks from many regions of the cerebral hemispheres, basal ganglia, brain stem and cerebellum were embedded in paraffin and stained with haematoxylin and eosin. Immunohistochemical (IHC) labelling was done with the avidin-biotin-complex peroxidase method, with diaminobenzidine as chromogen. Polyclonal antibodies were tested against the following antigens: Toxoplasma (Biogenex, San Ramon, Calif., USA),

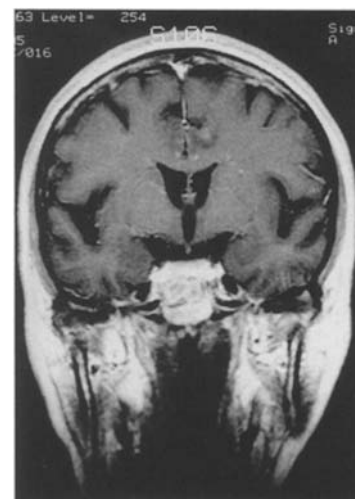
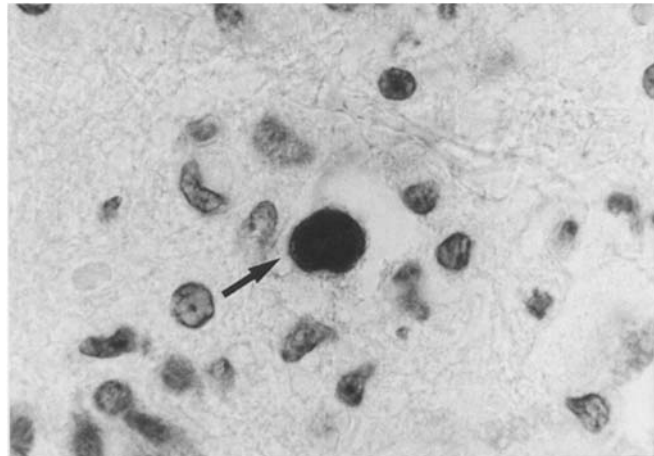


Fig. 1 Brain MRI showing a bicingular enhanced lesion (T1-weighted image), with no mass effect

Fig. 2 Immunohistochemistry for herpes simplex virus type 1 (HSV1): one neuron is strongly labelled (*arrow*). $\times 1250$



and HSV-1 and HSV-2 (Dako, Glostrup, Denmark), and monoclonal antibodies against CMV (CMV-13, Biosoft, Paris, France), varicella zoster virus (VZV; 2013, Biosoft) and HIV (p24, Cerlab, Paris, France). Controls included omission of the primary antibody and simultaneous staining of positive material. In situ hybridization (ISH) [3] was performed to detect HSV-1 and HSV-2 nucleic acid sequences with specific DNA probes corresponding to the isolated total genome, labelled with digoxigenin and developed with an alkaline phosphatase system. Gross examination of the brain showed limited bilateral necrosis of the cingulate gyri. A bilateral paramedian haematoma had destroyed the medulla-pons junction and extended to the right part of the pons, passing the midline up to the ponto-mesencephalic junction. There was no evidence of uncal herniation. Light microscopy showed perivascular inflammatory cells and numerous intranuclear inclusion bodies in neurons and glial cells, at the edges of the necrotico-haemorrhagic brain stem and cingulate lesions. Intranuclear inclusion bodies were also observed in ependymal and subependymal glial cells in the frontal horn of the lateral ventricles. IHC staining confirmed that these inclusions were HSV-1 (Fig. 2). Some neurons and glial cells in the same regions were faintly IHC stained for HSV-2. IHC staining for CMV, HIV and VZV was negative. ISH for HSV-1 gave a specific signal in the nuclei of neurons and glial cells, whereas no positive signal was detected with the HSV-2 DNA probe. In the wall of the fourth ventricle, 2 or 3 ependymal cells with CMV inclusions (IHC staining) were observed. The walls of blood vessels showed necrotizing changes and were infiltrated by polymorphonuclear leucocytes, notably at the edges of the necrotic haemor-

rhagic brain stem tissue. No other brain lesions, opportunistic infections, or multinucleated giant cells were seen.

This patient presented with a subacute brain stem syndrome characterized by bilateral fourth nerve palsy and hemiplegia without diffuse encephalitis. The brain stem lesion was firmly attributed to HSV-1 infection by IHC staining with a polyclonal antibody to HSV and ISH, and was the direct cause of death. Indeed, there was no compression of the midbrain by temporal lobe herniation that is frequently the ultimate cause of death in many cases of HSVE. Moreover, haemorrhagic lesions are quite frequent in HSVE, as in the case of Hamilton et al. [2] and that of Dayan et al. [6]. Haemorrhage is probably due to the brain tissue necrosis, haemorrhagic infarctions, and the extravasation of blood cells from altered blood vessels [6]. The patient had no past or concomitant skin eruptions consistent with HSV infection, unlike the case reported by Hamilton et al. [2].

The clinical manifestations and course of this patient raise issues concerning the diagnosis and pathogenesis of this kind of focal HSVE. The most common cause of bilateral fourth nerve palsy is a contrecoup injury to the decussation region after head trauma. No cases of fourth nerve palsy were described as a result of HSV infection in Keane's his-

torical and personal review [7]. The location of the encephalitis was highly atypical, in that the abnormalities were observed in the brain stem and the cingulate gyri, whereas HSVE usually involves the temporal lobes. There have been only five cases of autopsy-confirmed HSV brain stem encephalitis (reviewed in [2]), and only one case in an HIV-infected patient [2]. Such a distribution involving the brain stem and cingulate gyri has been reported once in an immunocompetent patient [8]. The pathogenesis of HSVE is speculative. As in experimental animals, brain stem infection might result from occult reactivation of latent trigeminal infections or active primary infections of the cranial ganglia [1, 2]. HSV genomes have also been detected by PCR in the medulla and pons, suggesting the presence of the virus in a latent state, even in the normal CNS [9]. Such results suggest a role for latent virus at this particular site, possibly reactivated by immunosuppression. The scarcity of reports of HSVE in AIDS has led to the suggestion that the neurological deficit in HSVE is due not so much to viral replication (cytotoxic neuronal changes) as to a severe virus-induced immuno-inflammatory response [1]. Such an immune reaction cannot be mounted in advanced AIDS. Nonetheless, the brains of mice inoculated with the clinical HSV-1 isolate by Hamilton et al. [2]

developed brain stem encephalitis, showing that some strains may be directly neurovirulent.

The devastating course in this patient, as in previous cases [1–3], underscores the need to consider HSV-1, as well as other herpes viruses like Epstein-Barr virus [10] and VZV [11], in the differential diagnosis of brain stem disorders in HIV-infected patients. PCR, now available in most university hospitals, holds out the promise of early and accurate diagnosis of HSVE [5]. Patients with HSVE have been reported to benefit from intravenous acyclovir therapy, and foscarnet may be used when there is resistance.

References

1. Tan SV, Guiloff RJ, Scaravilli F, Klapper PE, Cleator GM, Gazzard BG (1993) Herpes simplex type 1 encephalitis in acquired immunodeficiency syndrome. *Ann Neurol* 34:619–622
2. Hamilton RL, Achim C, Grafe MR, Fremont JC, Miners D, Wiley CA (1995) Herpes simplex virus brainstem encephalitis in an AIDS patient. *Clin Neuropathol* 14:45–50
3. Vital C, Monlun E, Vital A, et al (1995) Concurrent herpes simplex type 1 necrotizing encephalitis, cytomegalovirus ventriculoencephalitis and cerebral lymphoma in an AIDS patient. *Acta Neuropathol (Berl)* 89:105–108
4. Bredeisen DE, Levy RM, Rosenblum ML (1988) The neurology of human immunodeficiency virus infection. *Q J Med* 257:665–677
5. Rozenberg F, Lebon P (1991) Amplification and characterization of Herpesvirus DNA in cerebrospinal fluid from patients with acute encephalitis. *J Clin Microbiol* 11:2412–2417
6. Dayan AD, Goody W, Harrison MJG, et al (1972) Brain stem encephalitis caused by Herpesvirus hominis. *BMJ* 4:405–406
7. Keane JR (1993) Fourth nerve palsy: historical review and study of 215 inpatients. *Neurology* 43:2439–2443
8. Rose JW, Stroop WG, Matsuo F, Henkel J (1992) Atypical herpes simplex encephalitis: clinical, virologic, and neuropathologic evaluation. *Neurology* 42:1809–1812
9. Baringer JR, Pisani P (1994) Herpes simplex virus genomes in human nervous system tissue analysed by polymerase chain reaction. *Ann Neurol* 36:823–829
10. North K, De Silva L, Procopis P (1993) Brain-stem encephalitis caused by Epstein-Barr virus. *J Child Neurol* 8:40–42
11. Moulignier A, Pialoux G, Dega H, Dupont B, Huerre M, Baudrimont M (1995) Brain stem encephalitis due to Varicella Zoster Virus in an AIDS patient. *Clin Infect Dis* 20:1378–1380

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