**LETTERS**

**Medial medullary infarction with contralateral glossoplegia**

There is a relative lack of information on the course of corticohypoglossal projections in the human brainstem, especially in the medulla. Using transcranial magnetic stimulation and magnetic resonance imaging (MRI) in 11 patients with ischaemic lesions at different brainstem levels, Urban et al showed that pontine lesions at the ventral paramedian base close to the midline affected the contralateral corticohypoglossal projections, while lateral lesions at the pontine base affected the ipsilateral projections. Lesions of the dorsolateral and mediodorsal medulla impaired only ipsilateral corticohypoglossal projections.

We report a patient with contralateral glossoplegia in the ventromedial lesion of the upper medulla.

**Case report**

A 52 year old hypertensive man suddenly developed right sided paresthesia distal to the elbow and knee. The next day he had right hemiparesis. On neurological examination, he was found to have left beating nystagmus on left lateral gaze. Unilateral tongue paresis was demonstrated by voluntary protrusion, during which the tip of the tongue deviated to the right (fig 1A). When the tongue was not protruded, the right half of the tongue base was seen to bulge. Neither atrophy nor fasciculation was observed in the tongue. There were no abnormalities on tongue electromyography. He had mild right hemiparesis, mildly diminished sensation in all modes, which gradually worsened, and truncal ataxia. Brain MRI, done three days after symptom onset, showed an infarct in the ventromedial portion of the left rostral medulla extending deep into the dorsal portion (fig 1B and 1C). The paesthesiae and sensory deficits disappeared spontaneously in two weeks, and the limb weakness and the glossoplegia gradually improved, with complete resolution two months after stroke onset.

**Comment**

This patient's glossoplegia was a supranuclear palsy because the tongue deviated to the contralateral side of the lesion and neither atrophy nor fasciculation was observed. Protrusion of the tongue is accomplished by the unopposed action of the normal contralateral genioglossus. The corticobulbar fibres controlling the genioglossus muscles are crossed; the other tongue muscles appear to have bilateral supranuclear control. With regard to the supranuclear projections to the hypoglossal nucleus in the brainstem, it is still unclear at what level they decussate over the midline to reach the contralateral nucleus. Urban et al showed that lesions of the ventral pontine base located close to the midline only impair the contralateral corticohypoglossal projections, while lesions extending to the lateral part of the basis pontis and dorsolateral lesions of the upper medulla near the pontine border affect the ipsilateral projections. They suggested that the main decussation of these fibres is located close to the pontomesencephalic junction.

In this patient with contralateral supranuclear glossoplegia, the lesion was located on the ventromedial part of the rostral medulla. This finding shows that corticohypoglossal projections in this patient are decussated at the upper medullary level (fig 1D), more caudally than the pontomesencephalic junction described by Urban et al.

**Figure 1**

(A) The protruded tongue deviating to the right about 1.5 cm from the midline. Magnetic resonance imaging (T2 sagittal) and diffusion weighted (C) showed an acute unifocal ischaemic lesion in the left ventromedial part of the upper medulla. The schematic drawing (D) shows the proposed corticohypoglossal decussation at the upper medulla level.

**References**


**Recurrent hypertensive brainstem encephalopathy**

In hypertensive encephalopathy (HE), computerized tomography or magnetic resonance (MR) images usually exhibit predominantly posterior white matter involvement, similar to reversible posterior leukoencephalopathy syndrome (RPLS). Recurrent HE is rare. Here, we report a rare case of recurrent HE.

**Case report**

A 75 year old man with an unremarkable medical history presented with generalized convulsion and stupor following a headache in June 2003. On admission, his blood pressure (BP) was 200/120 mmHg. The T2 weighted MR images (T2WI) and fluid attenuated inversion recovery (FLAIR) images revealed hyperintense lesions and swelling in the brainstem (fig 1). There was no enhancement of these lesions after an
after blood pressure (BP) decreased, those findings disappeared spontaneously. (B) One year after the first admission, the FLAIR images revealed recurrent hyperintense lesions similar to those observed in the initial image. (C) One month later, after BP was found to be normotensive, the images revealed no abnormal findings.

Figure 1  Fluid attenuated inversion recovery (FLAIR) images of representative levels of the pons. (A) On the first admission, the FLAIR images revealed hyperintense lesions and swelling. After blood pressure (BP) decreased, those findings disappeared spontaneously. (B) One year after the first admission, the FLAIR images revealed recurrent hyperintense lesions similar to those observed in the initial image. (C) One month later, after BP was found to be normotensive, the images revealed no abnormal findings.
Diffuse cystic leucoencephalopathy after buprenorphine injection

Buprenorphine has been prescribed for opioid detoxification and subsequent maintenance therapy with favourable outcomes. Its high affinity for the mu receptor, higher analgesic potency than morphine, antagonistic effects at higher doses as a partial agonist, lower incidence of physical dependence, and mild withdrawal symptoms confer qualities that make it advantageous for the treatment of opioid dependence. Buprenorphine, marketed under the trade name Subutex, may be administered sublingually, subcutaneously, or intravenously. We describe a severe neurological effect of intravenous buprenorphine exposure that resulted in diffuse cystic leucoencephalopathy.

Case report

An 18 year old man was found unconscious in his bedroom by his girlfriend. He had no past history, and no family history of neurological or metabolic diseases. He was brought to the emergency room febrile, comatose and in severe respiratory failure (pH 7.399, pO₂ 84 mmHg, pCO₂ 42 mmHg, bicarbonate 24.9 mmol/L, on 100% non-rebreathing mask). He was intubated and treated presumptively for pneumonia with intravenous imipenam and azithromycin. He did not require inotropic support. Physical examination revealed a drowsy and lethargic man, who had bilateral basal crepitations in the lungs. Apart from midrange pupils that were sluggishly reactive to light, the neurological examination was unremarkable. There was no evidence of external bruises, injuries or obvious needle track marks over his arms. Initial investigations were significant for polymorphic leucocytosis (total white cell count, 8.08 x 10³/μL; polymorphonuclear leucocytes, 75%) and rhabdomyolysis (creatinine kinase, 8900 U/L; creatinine, 189 μmol/L). Serum and urine toxicology screen were positive for benzodiazepines.

Microbiological analysis of blood, urine, cerebrospinal fluid (CSF) and sputum samples did not yield any pathogens. Serology for Mycoplasma, Leptospira, and Rickettsia species, and influenza and Epstein-Barr viruses was negative. The patient’s condition improved and he was extubated 2 days later. Bilateral pyramidal dysfunction, with spastic quadriparesis, hypertonia, hyper-reflexia, sustained clonus and extensor plantar responses were noted 5 days later. pupils remained midrange and slowly reactive to light. He did not demonstrate any cranial neuropathies or cerebellar signs. Although bedside cognitive assessment was within normal limits, he was bradyphrenic. He did not manifest myoclonic jerking. Vibratory, proprioceptive, temperature and pinprick sensation were normal.

Brain CT scan and CSF examination were unremarkable (protein 0.39 g/L, glucose 3.6 mmol/L with normal cell counts and negative microbiological investigations including assays for neurotropic viruses). PCR for herpes simplex DNA in the CSF was negative and oligoclonal bands were absent. HIV and hepatitis B and C serologies were negative. Very long chain fatty acid and adrenocorticotropic hormone levels were normal. T2 weighted and fast fluid attenuated inversion recovery (FLAIR) sequenced magnetic resonance images (MRI) of the brain (fig 1) revealed diffuse leucoencephalopathy within the periventricular, deep and subcortical white matter of the frontal and parietal lobes. The cerebellum and brainstem were normal. An electroencephalogram showed seizure activity that resolved with diazepam and sodium valproate. Periodic sharp wave complexes were not observed. Nerve conduction, somatosensory, brainstem auditory, and visual evoked response testing were all within normal limits.

Gradually, the patient recovered the ability to move his limbs and engage in conversation. He confessed to misusing benzodiazepines for chronic insomnia and to having injected sublingual buprenorphine tablets, crushed and dissolved in water, intravenously into his right external jugular vein on the day of admission. An empty bottle of buprenorphine tablets by his bed and a scar in the neck bore testament to this. He received intensive rehabilitation, and MRI brain was repeated 2 weeks later. The T2 and FLAIR hyperintensities previously seen were more extensive, with new areas of cystic degeneration (fig 1). He was put on a course of oral baclofen and discharged with amelioration but not ablation of limb spasticity. Power was rated at MRC grade 4/5 in all four limbs at the time of discharge.

Discussion

The close temporal relationship of intravenous buprenorphine injection and symmetrical cystic leucoencephalopathy suggested to us a causal association. Intravenous buprenorphine was prepared in aqueous solution by crushing tablets of buprenorphine and dissolving them in water. We considered and excluded other differential diagnoses, such as acute disseminated encephalomyelitis (ADEM),...
adrenoleucodystrophy, multiple sclerosis, metachromatic leucodystrophy, progressive multifocal leukoencephalopathy, hypertensive leukoaraiosis, and hypoxic-ischemic brain damage based on the clinical picture. The normal cerebrospinal fluid (CSF) pressure, protein, white cell counts, and absent oligoclonal bands exclude ADEM and infective causes. Adrenoleucodystrophy was excluded by normal levels of serum cortisol, ACTH, and very long chain fatty acids. The clinical, neurophysiological, and neuroradiological picture was not suggestive of multiple sclerosis. The patient had no history of hypertension, and hypoxic-ischemic brain damage was unlikely, as the location of leukoencephalopathy was diffuse and not within the characteristic watershed territories. Genetic and metabolic causes of leukodystrophy could not be excluded, even though his normal neurocognitive development, mental history, late onset, the close temporal relationship with injection of buprenorphine, and the absence of family history make them unlikely.

The direct role played by buprenorphine in causing the diffuse leukoencephalopathy is not known. As mu opiate receptors are expressed both in the brain and immune system (in lymphocytes and phagocytes), the injected buprenorphine could possibly have triggered an immunological response to neural tissues within the brain, severely affecting areas that are susceptible to the effects of demyelination and ischaemia, such as the subcortical white matter, thus resulting in diffuse leukoencephalopathy. \(^2\) Although our patient denied the use of other recreational drugs, and repeated microbiological investigations did not reveal any pathogens, the possibility of impurities and additives present in the drug triggering an immunological and toxic reaction could not be excluded. The possibility of a synergistic effect on the metabolism of buprenorphine and benzodiazepine is raised as there has been reports of fatalities in patients receiving benzodiazepine and high dose buprenorphine.\(^3\)

Intentional misuse of detoxification drugs should be suspected in a patient who presents with diffuse leukoencephalopathy. Further studies are needed to explain our observation—that is, whether the leukoencephalopathy occurred as a direct effect of buprenorphine or as an indirect effect of impurities and additives present in the drug.

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References


Successful treatment of CMV ventriculitis immune reconstitution syndrome

In HIV infected patients, cytomegalovirus (CMV) disease of the central nervous system is usually seen when the CD4+ cell count is <100 cells/mm\(^3\). Recommended treatment includes intravenous ganciclovir, foscarinet, or both. Ventriculitis, however, is extremely rare. While Ventura et al. reported manifestations of CMV disease, mortality is extremely high despite timely initiation of treatment. Little is known about CMV ventriculitis in the highly active antiretroviral therapy (HAART) era.

Case report

A 38 year old woman with no significant past medical history was diagnosed with Pneumocystis jiroveci (Pneumocystis carinii) pneumonia as her AIDS defining illness in April 2002. On 15 July 2002, HAART was initiated with zidovudine, lamivudine, and efavirenz. Her CD4+ count was 42 cells/mm\(^3\) and her HIV-1 RNA level was 95 000 copies/ml. Serum CMV IgG was positive.

Ten days later, she was evaluated for headache of new onset. Computed tomography (CT) of her head was unremarkable. Cerebrospinal fluid analysis showed no white cells, a red cell count of 10/mm\(^3\), a protein level of 58 mg/dl, and a glucose of 40 mg/ml. Cryptococcal and histoplasma antigens were negative.

Two weeks later, after full compliance with her HIV therapy, she returned with headache, nausea, vomiting, and fever. Her temperature was 36.6°C (101.4°F). Neurological examination was normal and there was no meningism. Ophthalmological examination of the retinae with fully dilated pupils was normal.

The peripheral white blood count was 1 800 cells/mm\(^3\). Serum chemistry was normal. Cryptococcal and histoplasma antigens were negative. Bacterial, mycobacterial, and fungal blood cultures were sterile. Chest radiography and repeat head CT were normal. CSF analysis showed 13 white blood cells/mm\(^3\) (44% neutrophils, 23% lymphocytes, 12% monocytes), a red cell count of 4 cells/mm\(^3\), a protein level of 91 mg/dl, and a glucose of 30 mg/ml. Magnetic resonance imaging (MRI) of the brain showed abnormal contrast enhancement that of the ependymal lining around the ventricles, consistent with ventriculitis (fig 1). CSF herpes simplex virus polymerase chain reaction (PCR) was negative. Both CSF PCR and bone marrow culture were positive for CMV.

Ganciclovir (5 mg/kg intravenously twice daily) was initiated. Seven days later, the patient was afebrile, but noted only mild improvement in her headache, nausea, and vomiting. Therefore, intravenous foscarinet (90 mg/kg twice daily) was added; her symptoms resolved within 21 days of combined therapy. At that time, her CD4+ count was 159 cells/mm\(^3\) and the HIV-1 RNA level was <500 copies/ml. Follow up MRI showed improved appearance of the enhancement that was present at her initial diagnosis. CSF CMV PCR was subsequently negative. Valganciclovir (900 mg orally daily) for maintenance treatment was added to her HAART regimen. Three months after completing CMV induction therapy, the patient’s CD4+ count was 178 cells/mm\(^3\) and HIV-1 RNA was <50 copies/ml. Valganciclovir maintenance therapy was discontinued. There has been no recurrence of CMV disease over the 16 month period since discontinuing valganciclovir.

Comment

Several points in this case are noteworthy. The patient was diagnosed as having CMV ventriculitis three weeks after initiating HAART, during a period of immune recovery. While immune reconstitution syndromes (IRS) involving CMV retinitis and pneumonitis have been reported, to our knowledge an IRS with CMV ventriculitis has not been described previously. The time to onset of IRS associated with CMV infections ranges from weeks to several months. Our patient developed a headache with a normal laboratory evaluation after 10 days of treatment. Three weeks after initiating HAART, her illness progressed to include fevers, persistent headache, nausea, and vomiting. While we cannot absolutely exclude the possibility that her CMV ventriculitis was a coincidental infection of a susceptible individual, we believe the timing of her illness with recent initiation of HAART is more consistent with a CMV associated IRS. Our patient was CMV seropositive and therefore latently infected when HAART was initiated. Her CD4+ count increased from 43 to 159 cells/mm\(^3\) after 45 days of HAART. Additionally, between the 10th and 31st day of HAART, she developed CMV leucocytosis with progressive CSF protein elevation providing evidence of a significant CNS inflammatory reaction in a time interval consistent with IRS.

Studies addressing the best treatment for CMV ventriculoencephalitis in patients with AIDS are not definitive, although various comparative trials have addressed the treatment of retinitis. Current treatment options for CMV neurological disease include intravenous ganciclovir, intravenous foscarinet, or both. In a study of HIV infected patients with acute CMV infection of the CNS, combination foscarinet-ganciclovir therapy resulted in clinical improvement or stabilisation in 23 of 31 patients, but 10 of these had
significant side effects necessitating discontinuation of at least one drug. Our patient tolerated both fosarnet and ganciclovir for 21 days without significant side effects.

Given her initial presentation with advanced HIV-1 infection, we placed the patient on valganciclovir maintenance therapy (900 mg once daily) to prevent relapse of her CMV ventriculitis. In previous reports, maintenance therapy with intravenous ganciclovir prevented relapse of CMV encephalitis or myelitis in 13 of 23 AIDS patients. Linear regression analysis of data from CMV and HIV seropositive patients shows that valganciclovir, 900 mg once daily, produces target AUC24 values comparable to those achieved with intravenous ganciclovir at a dose of 5 mg/kg/day. Our patient with CMV ventriculitis or myelitis in 13 of 23 AIDS patients shows that

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