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CORRESPONDENCE

Vacuolar myelopathy: a case report of functional, clinical, and radiological improvement after highly active antiretroviral therapy

A 25-year-old black male with AIDS, who had a CD4 count of 9 cells/μl and a viral load of 31 000 copies/ml, presented in October 2006 with a 3-month history of weakness in both lower limbs. He was unable to walk unaided, and described 'pins and needles' in his legs and decreased sensation up to approximately thoracic dermatomal level 12. He described a dull lumbo-sacral backache with no sphincter dysfunction. He had a history of treatment for pulmonary tuberculosis in 2000.

On examination, he was cachectic with generalized lymphadenopathy and oral thrush. He was apyrexial and normotensive with a pulse rate of 86 beats/min. He was lucid and did not display any neck stiffness. Examination of the cranial nerves and upper limbs was normal apart from proprioceptive loss in the upper limbs. The tone in his lower limbs was increased and the power in his lower limbs was Medical Research Council scale (MRC) grade 4. The knee reflexes were brisk but the ankle reflexes were diminished. The plantar responses were extensor bilaterally. He had global joint position sense loss and had a thoracic dermatomal sensory level of 9 to pinprick and light touch.

In view of his marked immunosuppression and clinical presentation, the diagnosis of vacuolar myelopathy was suspected. Further blood investigations and magnetic resonance imaging (MRI) was done to confirm the diagnosis and exclude other causes of HIV-associated myelopathy, from opportunistic infections to neoplasms.

Blood investigations showed normal vitamin B_{12} and folate levels, a normocytic normochromic anemia, and negative screens for toxoplasmosis and syphilis. Cerebrospinal fluid examination showed no cells and normal chemistry. MRI of the entire cord revealed no intra- or extradural masses. However there was a prominent T2 hyperintensity of the posterior columns extending from the upper cervical to lower thoracic cord. No contrast enhancement was noted. The features were consistent with vacuolar myelopathy (see Figures 1 and 2).

MRI features of vacuolar myelopathy are well described and on axial views appear as high intensity lesions involving the posterior columns. A peripheral axonal neuropathy is a common accompaniment of vacuolar myelopathy and probably reflects the degree of immunosuppression in patients, rather than sharing a common pathophysiology.

Vacuolar myelopathy is a common form of spinal cord disease in HIV positive patients.[1] Petito et al. performed an autopsy-based study, which revealed that 20/89 (22%) patients had vacuolar myelopathy.[1,2] An even higher prevalence of 46.5% was reported by Dal Pan et al. Despite this high frequency, only 26.8% of patients with autopsy-proven vacuolar myelopathy had signs and symptoms.[3] Vacuolar myelopathy is often accompanied by other neurological disorders associated with advanced AIDS, and this may explain why it is often clinically under-recognized.[1]

Pathologically, vacuolar myelopathy is characterized by intralamellar vacuolation in the spinal white matter throughout the lateral and posterior columns of the thoracic and, occasionally, the cervical segments of the spinal cord.[1,4,5] There are a few theories concerning the pathophysiology of vacuolar myelopathy. These include: infiltration by neurotoxic cytokines, direct HIV infection of astrocytes and neurons, neurotoxic HIV proteins, and the impaired ability to utilize vitamin B_{12} as a source of methionine in transmethylation metabolism for myelin maintenance in the spinal cord.[6]

Vacuolar myelopathy is a diagnosis of exclusion, and other spinal cord diseases (both infectious and non-infectious causes), which may mimic this condition, must be ruled out. Vitamin B_{12} deficiency occurs in 13—50% of HIV infected individuals.[7—9] Subacute combined degeneration of the spinal cord in the presence of normal vitamin B_{12} levels (and megaloblastic anemia) has been described.[10] This patient had no predisposing factors to vitamin B_{12} deficiency except for HIV infection, and in the absence of vitamin B_{12} replenishment the myelopathy improved. This supports a diagnosis of vacuolar myelopathy with response to highly active antiretroviral therapy (HAART) rather than B_{12} deficiency-associated subacute combined degeneration of the spinal cord.

The manifestation of vacuolar myelopathy is varied and often presents as a painless spastic paraparesis that is slowly progressive, with a sensory ataxia.[5] There may be an associated sphincter and erectile dysfunction. Overlapping peripheral neuropathy may provide a diagnostic challenge.[1] Hyperreflexia at the knees is a common finding with reduced ankle reflexes.[1] Back pain is not common and a discrete sensory level if present suggests an alternative cause of myelopathy.[6] In our patient however, in the absence of an alternative cause

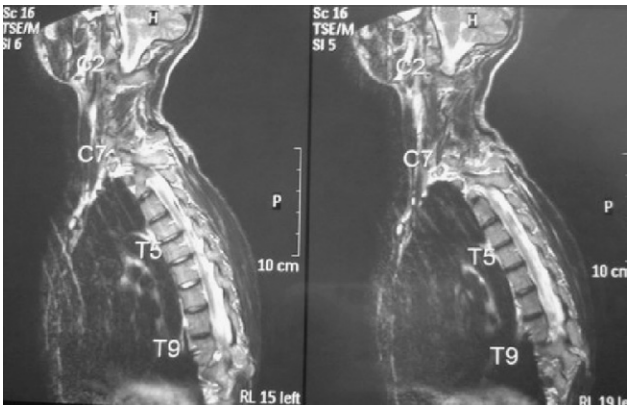

Figure 1 T2 sagittal thoracic spine: pre-treatment.

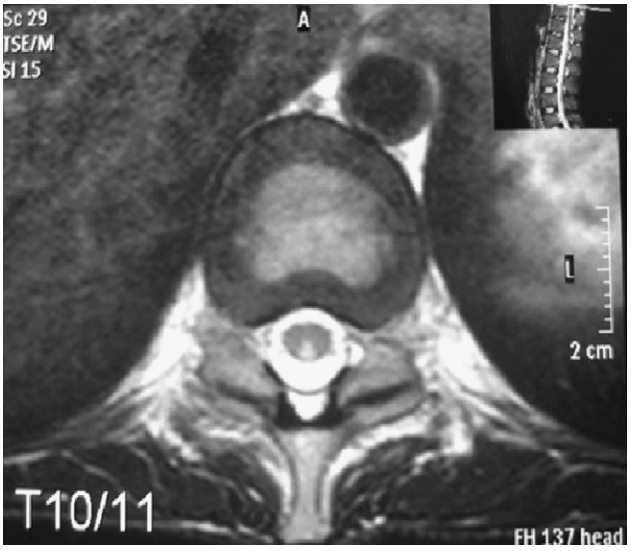

Figure 2 T2 axial spine: pre-treatment at T10/11. Hyperintense posterior columns demonstrated. Note: trefoil appearance of hyperintensity.

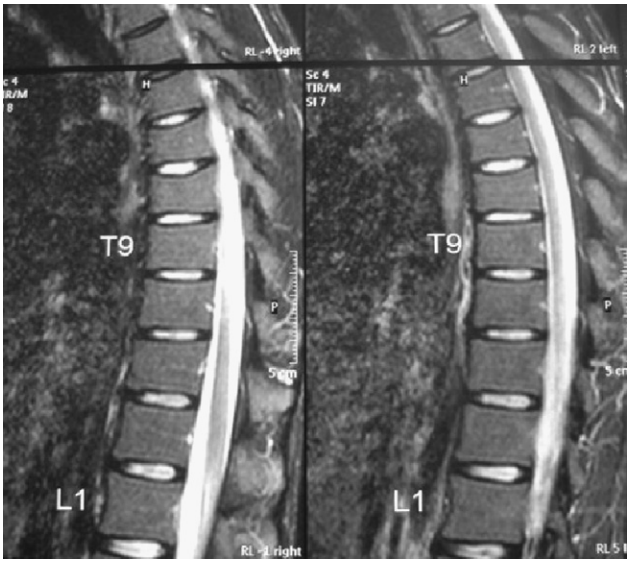

Figure 3 T2 sagittal thoracic spine: post-treatment.

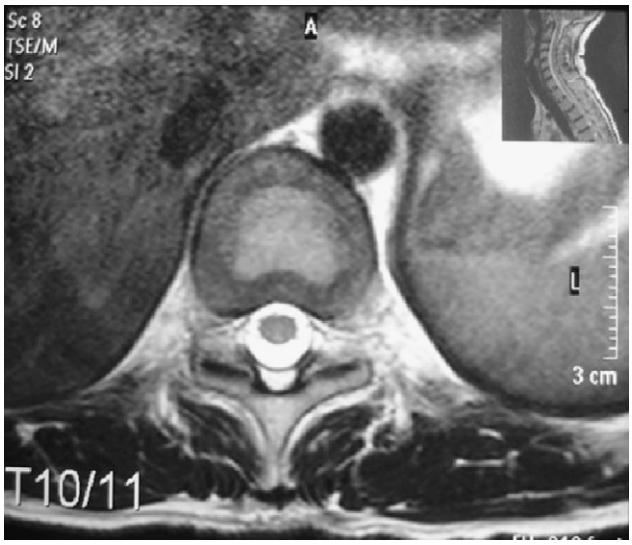

Figure 4 T2 axial spine: post-treatment. Significant reduction in T2 hyperintensity of posterior column.

we feel his low backache and crisp sensory level had to be associated with his diagnosis of vacuolar myelopathy.

The treatment of vacuolar myelopathy is uncertain; it is mainly supportive and HAART is believed to improve the prognosis.[4] In addition there have been anecdotal case reports of improvement on HAART.[4,6] This patient was started on HAART (regimen 1a: stavudine, lamivudine, and efavirenz) shortly after discharge. Seven months later the patient has made a remarkable recovery. Whilst his CD4 count increase is modest, just 87 cells/μl, his viral load is $<$25 copies/ml, his weight has increased by 15 kg, and he now walks unaided. In addition, his neurological examination has revealed normal joint position sense in the upper limbs and mild impairment in the lower limbs. The glove and stocking sensory impairment and the peripheral neuropathy persist and are being treated symptomatically.

Repeat MRI of the spine following 7 months of HAART has revealed significant reduction of the T2 hyperintensity of the posterior columns noted on the pre-treatment films (see Figures 3 and 4).

This case report supports other anecdotal reports of the benefit of HAART in vacuolar myelopathy and highlights the need for case—controled studies to investigate qualitatively and quantitatively the role of HAART in the management of vacuolar myelopathy.

Conflict of interest: No conflict of interest to declare.

References

1. Di Rocca A. HIV associated myelopathy. *Curr Treat Options Infect Dis* 2003;**5**:457—65.
2. Petito CK, Navia BA, Cho ES, Jordan BD, George DC, Price RW. Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1985;**312**:874—9.
3. Dal Pan GJ, Glass JD, McArthur JC. Clinicopathologic correlations of HIV associated vacuolar myelopathy: an autopsy based case—control study. *Neurology* 1994;**44**:2159—64.

4. Fernandez-Fernandez FJ, de la Fuente-Aguado J, Ocampo-Hermida A, Iglesias-Castanon A. Remission of HIV-associated myelopathy after highly active antiretroviral therapy. *J Postgrad Med* 2004;**50**:195–6.
5. McArthur JC, Brew B, Nath A. Neurological complications of HIV Infection. *Lancet Neurol* 2005;**4**:543–55.
6. Singh NN, Thomas FP. HIV-1 associated vacuolar myelopathy. *eMedicine-WebMD*. March 2007. Available at: http://www.emedicine.com/NEURO/topic449.htm (accessed November 2007).
7. Hepburn MJ, Dyal K, Runser LA, Barfield RL, Hepburn LM, Fraser SL. Low serum vitamin B12 levels in an outpatient HIV-infected population. *Int J STD AIDS* 2004;**15**:127–33.
8. Remacha AF, Codafalch J, Sarda P, Barcelo M, Fuster M. Vitamin B12 metabolism in HIV-infected patients in the age of highly active antiretroviral therapy: role of homocysteine in assessing vitamin B12 stores. *Am J Clin Nutr* 2003;**77**:420–4.
9. Swagel E. The elusive (and maybe non-existent) connection between vitamin B12 and HIV. *Nutrition Bytes* 1996; **2**:Article 4. Available at: http://repositories.cdlib.org/uclabiolchem/nutritionbytes/vol2/iss2/art4 (accessed November 2007).
10. Nagaishi A, Takashima H, Fukuda Y, Kuroda Y. [A case of subacute combined degeneration with normal serum vitamin B12 level] (in Japanese). *Rinsho Shinkeigaku* 2003;**43**:552–5.

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Acute liver failure due to dengue virus infection

Acute liver failure is a condition in which there is rapid deterioration of liver function, resulting in hepatic encephalopathy and/or coagulopathy.[1] In Latin America, complicated forms of certain tropical infections such as *Plasmodium falciparum* malaria, leptospirosis, rickettsial fever, typhoid fever, viral hepatitis, and rarely dengue, may present as acute liver failure. Early identification of these infections is important in reducing morbidity and mortality.[2]

A 31-year-old previously healthy female presented at our clinic with a 3-day history of fever, myalgia, bilirubinuria, arthralgia, and altered mental status. She denied having any previous history of dengue or malaria. Physical examination disclosed a diffuse maculopapular rash, asterixis, and jaundice. Ten days prior to her admission she had traveled to Tolima, Colombia, a hyperendemic area for dengue infection where an ongoing outbreak due to DEN-2 (dengue virus serotype 2) was taking place. Laboratory investigations on admission showed a normal white blood cell (WBC) count and mild thrombocytopenia; blood chemistries demonstrated a bilirubin of 8.1 mg/dl, AST of 2876 UI/l, and ALT of 2120 UI/l. Her international normalized ratio (INR) was 4.47 with a prolonged prothrombin time (PT) and a prolonged partial thromboplastin time (PTT). Thick and thin smears for malaria and blood cultures were negative. Diagnostic testing for hepatitis A (IgM), hepatitis B (HBsAg, HBV DNA PCR), hepatitis C (IgG, HCV RNA PCR), hepatitis E (IgM, IgG), yellow fever (RNA PCR), *Rickettsia spp* (IgM/IgG), Epstein–Barr virus, cytomegalovirus, parvovirus B19 (IgM, IgG), HIV (RNA PCR), and leptospirosis (ELISA IgM and MAT) were all negative. Her dengue IgM titers were positive at high titers. There was no evidence of dengue hemorrhagic fever. A diagnosis of acute liver failure due to dengue was then made. Despite supportive efforts, our patient progressed to multiorgan failure and subsequently died.

The clinical spectrum of dengue infections ranges from asymptomatic infection, to dengue fever (DF), to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DHS).[2,3] However, sometimes dengue may manifest with atypical clinical presentations such as acute liver failure. Indeed, up to 90% of patients with DF may develop mild to moderate elevation of liver transaminases with higher levels of AST.[4,5] Liver involvement in DF and DHF has been described in Asia and the Pacific Islands, and more recently in the Americas.[4–6] However, acute liver failure has rarely been reported in the setting of DF, and most of these reports have occurred in children with DHF and have frequently been associated with DEN-3 (dengue virus serotype 3) infection.[4–6]

Dengue virus liver injury may occur due to its ability to replicate in liver cells leading to hepatocellular injury with development of Councilman bodies.[7,8] In fact, in situ detection of DNA fragmentation and apoptotic hepatocytes in association with dengue virus-infected hepatocytes has suggested that hepatocytes are important sites of viral replication and that dengue virus induces apoptosis in vivo.[7]

Our case demonstrates that in addition to classic DF and DHF, testing for dengue should also be pursued among travelers returning from tropical areas endemic for dengue presenting with acute liver failure.

Conflict of interest: No conflict of interest to declare.

References

1. Deepak NA, Patel ND. Differential diagnosis of acute liver failure in India. *Ann Hepatol* 2006;**5**:150–6.
2. Wilder-Smith A, Schwartz E. Dengue in travelers. *N Engl J Med* 2005;**353**:924–32.
3. Gomez Mourao MP, Guimaraes de Lacerda MV, de Souza Bastos M, de Albuquerque BC, Duarte Alecrim W. Dengue hemorrhagic fever and acute hepatitis: a case report. *Braz J Infect Dis* 2004;**8**:461–4.