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Case report

Human T-lymphotropic virus type I or II (HTLV-I/II) associated with recurrent longitudinally extensive transverse myelitis (LETM): two case reports

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We describe two patients with recurrent longitudinally extensive transverse myelitis (LETM) associated with human T-lymphotropic virus type I or II (HTLV-I/II) exposure, and with neuromyelitis optica (NMO) immunoglobulin G (IgG) antibody in one case. HTLV-I/II are well known retroviral agents of myelopathy and B-cell dysfunction in humans. NMO is an autoimmune, demyelinating disorder of the central nervous system (CNS), also linked to B-cell dysfunction. Therefore, the immunopathogenesis of NMO may in some cases be linked to human HTLV exposure. Awareness of a possible association with human retroviral exposure will contribute to the optimal diagnosis and management of patients presenting with LETM or NMO. *Journal of NeuroVirology* (2010) **16,** 249–253.

Keywords: NMO; neuromyelitis optica; Devic's disease; HTLV-I/II; myelopathy; CNS demyelinating diseases; longitudinally extensive transverse myelitis

Background

Neuromyelitis optica (NMO), also known as Devic's disease, is a severe, inflammatory, necrotizing demyelinating disorder affecting the optic nerves and long segments of the spinal cord (Wingerchuk, 2007). The NMO disease spectrum includes longitudinally extensive transverse myelitis (LETM) (Wingerchuk, 2006; Wingerchuk *et al*, 2007). LETM is defined by spinal cord lesions extending contiguously over three or more vertebral segments, as seen on sagittal views with magnetic resonance imaging (MRI). In acute episodes, cord lesions are usually gadolinium-enhancing and may be associated with edema and cord expansion.

NMO appears to be a B cell–mediated disease associated with serum autoantibodies. In 50% to 73% of cases, there is serum immunoglobulin G (IgG) antibody directed against the water channel aquaporin-4 antigen (NMO-IgG). Half of NMO cases are associated with other autoantibodies such as antinuclear antibodies (ANAs) (Wingerchuk, 2007).

Human T-lymphotropic virus type I (HTLV-I) is a lymphotropic retrovirus that globally infects some 20 million individuals. Approximately 2% to 5% of these develop a progressive myelopathy known as HTLV-I–associated myelopathy (HAM), which overlaps tropical spastic paraparesis (TSP) (Araujo and Silva, 2006). HTLV-I infection has also been associated with systemic autoimmune diseases, including polymyositis, uveitis, and Sjögren syndrome (Morgan *et al*, 1989; Mochizuki *et al*, 1992; Vernant *et al*, 1987). Immune abnormalities accompany HAM/TSP, including autoantibodies, increased plasma or spinal fluid levels of inflammatory cytokines, and spontaneous lymphoproliferation, which occurs in both HAM/TSP and with HTLV-II infection (reviewed in Jacobson, 2002). HTLV-II infection has been associated with spastic paraparesis similar to HAM/TSP (Jacobson *et al*, 1993), and with spastic ataxia (Harrington *et al*, 1993). HTLV-II is epidemic among intravenous drug (IV) drug users worldwide (Araujo and Hall, 2004).

Most HTLV-1–infected individuals will remain clinically asymptomatic. The 2% to 5% who develop HAM/TSP tend to have very high HTLV-I proviral

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load compared to asymptomatic carriers (Araujo and Hall, 2004). HAM/TSP usually has a slow onset with chronic progression; neurological impairment develops within the first 2 years. The progression of neurological deficit can be accelerated by higher proviral load (Araujo and Silva, 2006), or prior blood transfusion (Sheremata *et al*, 1992). Acute onset with rapid progression of HTLV-1–associated myelopathy has been termed "acute HAM" (Kashahata et al, 2003). Acute HAM involves extensive spinal cord lesions, swelling of the cord, and vacuolation in the white matter (Kasahata *et al*, 2003). Thus the diagnosis of acute HAM may be confounded by other etiologies such as multiple sclerosis or NMO (Koga *et al*, 2009).

The relationship between NMO spectrum disorders and human retrovirus infection has yet to be fully defined. There are two reported cases supporting a connection between NMO and retroviral infection, including human immunodeficiency virus (HIV) (Blanche *et al*, 2000) and HTLV-I (Koga *et al*, 2009). We report two cases in which recurrent LETM is associated with HTLV-I/II exposure, including one case with serum NMO-IgG antibody.

Case 1

A 61-year-old female, wife of an intravenous drug user, developed Lhermitte's sign followed by rapid onset of tetraparesis in March 1996. After treatment for acute transverse myelitis with intravenous corticosteroids and intravenous immunoglobulin (IVIg), she had a full functional recovery over 3 months. Three years later, she had a second episode of transverse myelitis presenting with Lhermitte's sign, rapidly progressive paraplegia, loss of bladder and bowel functions, severe burning pain in her legs, and a band-like sensation around her chest at the T3–T4 level. MRI showed a cord lesion extending from C3 to T7. She was treated with intravenous corticosteroids and IVIg. She was diagnosed with multiple sclerosis based on relapsing myelitis, and treated with interferon-β 1b. She improved slowly over 3 to 4 months, and was able to work for a short period of time. She developed an allergic-type reaction (hives) on interferon-β 1b, and was then treated with glatiramer acetate and interferon-β 1a (intramuscular). When she continued to have relapses, she was treated with four doses of mitoxantrone, from June 2003 through January 2004. MRI of cervical and thoracic spine then showed a syrinx from C3 to T7.

In 2005, she was referred to our center for evaluation of syrinx and subarachnoid cyst with associated cord atrophy from T1 to T5. The patient underwent T2–T5 laminectomy and duraplasty of the spinal cord in October 2005 with good recovery. She was able to walk independently after 2 months. Four months after surgery, she experienced the recurrence of the band-like sensation around her chest, Lhermitte's sign, urinary retention, and weakness of the legs that would progress to paraplegia over the next several months despite treatment. Her neurological examination revealed a T9 sensory level to pain and temperature sensation. Vision was 20/100 OD and 20/30 OS (corrected), with normal fundoscopic examination. Visual evoked potentials (VEP) were not done. MRI studies showed normal brain (not shown), but extensive hyperintense T2-weighted signal within the spinal cord from C4 to T6; this segment enhanced with gadolinium

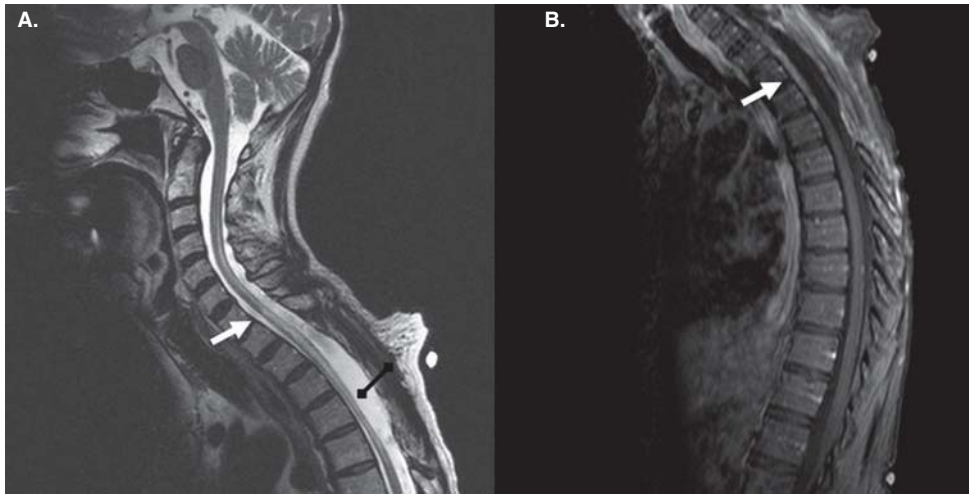

Figure 1 Case 1, MRI of cervical and upper thoracic spine. (**A**) T2-weighted sagittal view showed extensive increased signal in the cord extending from C4 level inferiorly, involving both the central cord at some levels and dorsal cord at others. The thoracic cord showed signal abnormality extending from T1 (*white arrow*) to T6, and a large cyst (*black diamondhead arrow*) consistent with an intradural arachnoid cyst from T2 to T5 causing mass effect on the cord. (**B**) T1-weighted sagittal view postcontrast showed corresponding abnormal enhancement within the thoracic cord (*white arrow*).

contrast (Figure 1). Serum NMO-IgG antibody was detected, as well as serum and cerebrospinal fluid (CSF) antibody to HTLV-II. Serum HTLV-II antibodies reacted with p24, GD21, and rgp46-II proteins by Western blot analysis. CSF had 6 white cells/mm^3, a total protein of 55 mg/dl, and no oligoclonal bands. CSF cytology evaluation did not detect malignant cells. Serum rapid plasmin reagin (RPR) and CSF Venereal Disease Research Laboratory (VDRL) test were nonreactive. Serum antinuclear antibody (ANA) was detected with titer 1:40 (homogeneous pattern). Rheumatoid factor and Sjögren's antibodies were not detected. Vitamin B_{12}, folate, and angiotensin-converting enzyme (ACE) levels were normal. The inflammatory markers C-reactive protein (CRP) and Westergren erythrocyte sedimentation rate (ESR) were mildly increased at 3 mg/dl (normal: <1.0) and 30 mm/h (normal: 1–20), respectively. The patient was treated with plasma exchange, intravenous corticosteroids, and rituximab. She was followed for the next 5 months; there was no neurological improvement.

Case 2

A 51-year-old Jamaican male developed severe neck pain with burning and weakness of the right hand. MRI of cervical spine reportedly showed a lesion in the cervical cord. Systemic corticosteroid treatment led to functional improvement, but 3 months later he developed numbness of the distal lower extremities followed by a right foot drop. Severe neck pain was followed by right hemiparesis 1 month later. He became paraplegic and developed urinary retention. MRI of the cervical spine reportedly then showed a cervical cord lesion extending from C2 to C7, with contrast enhancement and cord expansion. He was treated with IV corticosteroid (dexamethasone) for several days, then transferred to our center 2 weeks later. His neurological examination showed a prominent right hemiparesis with absence of proprioception in the right upper extremity and in both legs. Gait was ataxic. His visual acuity was 20/40 OU without correction. The patient did not have VEP.

Diagnostic evaluation found serum antibody to HTLV-I, with reactivity to viral p19 protein on Western blot analysis. CSF had 0 white cells/mm^3, mildly elevated total protein of 60 mg/dl, no oligoclonal bands, and normal IgG level. Serum RPR was reactive with titer 1:16, but CSF VDRL test was nonreactive. Serum ANA was detected with titer 1:160 (nucleolar pattern). Sjögren's syndrome antibodies and HIV-1–specific antibodies were not detected. Serum ACE level was normal at 42 U/L (normal: 9–67). ESR was mildly elevated at 37 mm/h (normal: 1–20). NMO antibody test was not available at the time.

The patient received 3 days of IV corticosteroid (methylprednisolone at 1 g daily). MRI of brain showed nonspecific, punctuate areas of hyperintense signal within the bifrontal, subcortical, and posterior left periventricular white matter on T2-weighted images. There was no enhancement with contrast. MRI of the cervical spine revealed an intramedullary lesion extending from C2 to C7 with associated cord expansion (Figure 2A). The patient was further treated with first IV then oral corticosteroids (prednisone) plus α-interferon for 6 months. His gait recovered, but he remained with right hemibody ataxia and mild spasticity.

MRI of cervical spine 4 months later showed atrophy and abnormal T2 prolongation along the dorsal columns of the cervical cord from C3 to C6 (Figure 2B). There was no enhancement with contrast. This patient was followed for 6 months with stable right hemibody ataxia and mild spasticity.

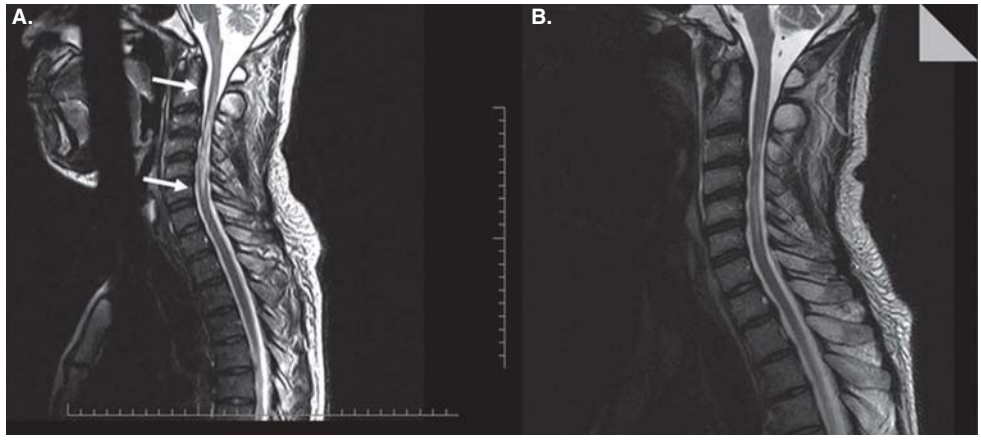

Figure 2 Case 2. (**A**) MRI of cervical and upper thoracic spine. T2-weighted sagittal view showed increased signal within the cervical cord extending from C2 to C6–C7 (*white arrows*), with associated cord expansion. (**B**) MRI of cervical and upper thoracic spine performed 4 months after scan in **A**. T2-weighted sagittal view showed cord atrophy and increased signal within the cervical cord extending from C3 to C6.

Discussion

We report two cases of recurrent LETM associated with exposure to human T-lymphotrophic viruses, HTLV-I or HTLV-II. In the case with HTLV-II antibody, serum NMO-IgG antibody was detected. In the other case, NMO antibody testing was not available. The patient had recurrent episodes of LETM, with cord lesions associated with edema and cord enlargement. He had incomplete but significant neurological recovery in response to treatment. Thus, this patient's clinical picture was consistent with LETM within the spectrum of NMO (Wingerchuk *et al*, 2007).

As NMO is a B cell–mediated disease associated with autoantibodies, the possible association of HTLV-I/II with NMO is provocative. Thus far there is one case report of NMO with HIV-1 retroviral infection (Blanche *et al*, 2000), and another recent report of NMO with HTLV-I retroviral infection (Koga *et al*, 2009). The HTLV-I/II retroviruses are known viral associates of human myelopathy, and there is evidence that patients with HTLV-associated myelopathy may have humoral dysfunction and increased incidence of other autoimmune diseases mediated by B cells (Mochizuki *et al*, 1992; Morgan *et al*, 1989; Vernant *et al*, 1987; Jacobson, 2002). Molecular mimicry between HTLV-I Tax protein, a transactivator of cellular genes, and a neuron-specific autoantigen (heterogeneous nuclear ribonuclear protein A1) has been implicated in the pathogenesis of HAM/TSP (Takenouchi *et al*, 2004). HTLV-1 infection also stimulates up-regulation of proinflammatory cytokines (Jacobson, 2002). This could potentiate epitope spread, which could eventually generate NMO-type autoantibodies.

NMO-IgG assay has only recently become a very useful tool for the diagnosis of NMO (Lennon *et al*, 2004; Wingerchuk, 2007). Prior to the availability of this test, patients with LETM and serum HTLV antibodies were not routinely tested for NMO. Similarly, patients with recurrent LETM or NMO have not been routinely tested for HTLV antibodies, although HTLV-1 can cause optic neuritis and atrophy (Araujo and Silva, 2006). Acute HAM could also confound the diagnosis of patients presenting with LETM or NMO. Acute HAM could be an aggressive form of HTLV-associated myelitis caused by infection with a high viral load, such as with contaminated blood transfusions or IV drug injections (Sheremata *et al*, 1992). Thus HTLV-associated myelopathy may have a wider clinical spectrum than was originally thought (Umehara *et al*, 2007).

Clinical overlap can make the differential diagnosis of HAM/TSP and NMO/LETM a challenge. MRI imaging may be useful to distinguish these entities (Table 1). Cord lesions in HAM/TSP are variable (Umehara *et al*, 2007). Lesions can occur in cervical or thoracic spinal cord, associated with or without contrast enhancement and cord swelling. The MRI hallmark of HAM/TSP is cord atrophy, mainly at the thoracic level, and appearing several months after clinical onset. Our case 2 showed cord atrophy 5 months after recurrent myelitis (Figure 2B). The MRI hallmark of NMO is cord lesions extending three or more vertebral segments. Unlike multiple sclerosis (MS) and like NMO, nonspecific brain white matter lesions occur in HAM/TSP (Godoy *et al*, 1995). Kira et al (1991) reported that brain white matter lesions were significantly more frequent in HAM/TSP patients compared to HTLV-I–seropositive carriers (37% versus 10%, respectively). But more recently Morgan et al (2007) reported no significant differences in brain white matter lesions between the two groups.

The cases we describe herein suggest that HTLV-associated myelopathies presenting with LETM may be included in the NMO spectrum disorders. Patients presenting with LETM and/or NMO should be

Table 1 Characteristics of multiple sclerosis (MS), neuromyelitis optica (NMO), and HAM/TSP

	MS	NMO	HAM/TSP
MRI brain	Periventricular white matter lesions, corpus callosal (Dawson's fingers)	Normal, nonspecific WM lesions, subcortical hypothalamic, brainstem, periependymal	Nonspecific periventricular and subcortical WM lesions
MRI spinal cord	Small (<3 vertebral segments), dorsolateral lesions Acute lesions are contrast-enhancing	Extensive (≥3 vertebral segments) usually with edema and cord expansion if acute lesions Central cord lesions	Variable spinal cord atrophy (hallmark) mainly at the thoracic level, in later stages Cervical or thoracic spinal cord lesions Diffuse abnormal T2 lesions w/wo cord swelling and contrast enhancement Usually dorsolateral lesions
Disease course	Relapsing-remitting (85%)	Relapsing (80–90%)	Progressive
CSF findings	Mild pleocytocis (mononuclear cells) Oligoclonal bands positive (85%)	Occasional prominent pleocytosis (neutrophils) Oligoclonal bands positive (15–30%)	Mild pleocytosis (mononuclear) Oligoclonal bands can be positive

Note. HAM/TSP, HTLV-I–associated myelopathy/tropical spastic paraparesis; WM = white matter.
Modified from Wingerchuk *et al*, 2007; Araujo and Silva, 2006; Umehara *et al*, 2007.

evaluated for serum HTLV-I and -II antibodies. Patients with HTLV antibodies should have a proviral load assay to detect active viral infection. Patients with active viral infection could be considered for antiviral treatment with interferon (Unsong *et al*, 2005; Izumo *et al*, 1996) in addition to immunomodulating therapy usually recommended for NMO, although interferon therapies have not been proven effective in NMO (Wingerchuk and Weinshenker, 2008). Ultimately, the patient's clinical evolution and response to treatment will clarify the final diagnosis in patients with both HTLV and NMO antibodies. Awareness of the potential association with human retroviral myelopathy will contribute to accurate diagnosis and a better understanding of the spectrum of disorders presenting with LETM or NMO.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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