Pearls & Oy-sters: "Not multiple sclerosis" and the changing face of HTLV-1

A case report of downbeat nystagmus

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PEARLS

- In the absence of typical clinical and radiologic features suggestive of MS, all other mimics of demyelinating disease need to be thoroughly excluded.
- HTLV-1 infection has been reported to cause extraspinal neurologic manifestations and should be included in the evaluation of suspected demyelinating disease, both of brain and spinal cord.
- Since HTLV-1 is known mainly to cause spinal cord atrophy, no imaging abnormalities may be seen in early stages of infection. Atrophy and magnetic resonance signal changes may be seen during advanced stages of the disease.
- CSF HTLV-1 may be negative by ELISA in 20% of cases despite serum studies being positive. Consider repeat testing in such cases.

Human T-cell lymphotropic virus–1 (HTLV-1) is endemic in Southern Japan, the Caribbean, and parts of western Africa, the Middle East, South America, and Melanesia.[1] HTLV-1 has a proven association with HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), adult T-cell leukemia, and uveitis.[1,7] Some reports indicate a possible association with dermatitis, polymyositis, arthritis, pneumonitis, and Sjögren syndrome. The most widely reported neurologic manifestation of this condition is slowly progressive myelopathy, which may clinically resemble primary progressive multiple sclerosis (MS).[1,7,8] Extraspinal manifestations have been mostly limited to case reports and include cerebellar tremor, cognitive impairment, leukoencephalopathy, and optic neuritis.[2] Cerebellar symptoms as a presenting feature of HTLV-1 are rare.[3] On extensive literature search, we found a case report of a Japanese woman with HTLV-1 presenting with downbeat nystagmus and cerebellar vermian atrophy.[4] Another report from Scandinavia discusses three patients with HTLV-1-associated spinocerebellar syndrome.[3] Overall, there have been nearly 14 cases of HTLV-associated cerebellar involvement reported from Japan and Canada.

CASE REPORT A 52-year-old African American woman with a history of benign paroxysmal positional vertigo and hypertension presented with worsening episodes of vertigo at rest. She had the onset of bowel and bladder incontinence 2 years preceding the onset of her vertigo. Her cognitive function was normal. Neurologic examination revealed primary position vertical pendular nystagmus with a strong downbeating vector. Her extraocular movements were intact. Tone and strength of her extremities was normal. Deep tendon reflexes were diffusely brisk with flexor plantars. She had intact sensation to all modalities. Gait was wide-based. No appendicular dysmetria was noted.

Electronystagmography showed primary position vertical pendular nystagmus with a fast downbeating vector, most consistent with a central origin (figure). Nystagmus dampened with downgaze and increased on upgaze (in opposition to Alexander's law, according to which the amplitude of nystagmus increases with gaze in the direction of the fast phase). There was no effect of convergence on the nystagmus. Some adduction slowing was seen bilaterally from eccentric gaze to center target, suggesting the possibility of internuclear ophthalmoparesis, and implicating an occult lesion of the medial longitudinal fasciculus.

Brain MRI showed a few discrete juxtacortical white matter lesions. There were no lesions perpendicular to the ventricle typical for MS. Brainstem images including T2 sequences were unremarkable. MRI of the spine was unremarkable.

CSF showed a remarkably elevated immunoglobulin G (IgG) index of 2.08 (normal range: 0.3 to 0.7), an IgG synthetic rate of 27.88 (normal range: <3), and oligoclonal bands. CSF angiotensin con-

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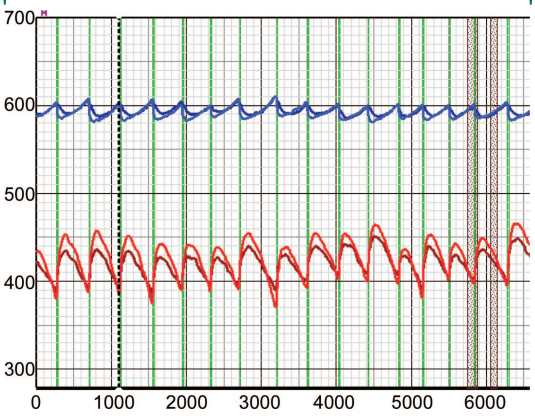
Figure Screen capture of nystagmus at primary position



The upper two lines represent recordings from the horizontal channel and the lower two lines from the vertical channel.

verting enzyme (ACE) and VDRL results were unremarkable. Serum erythrocyte sedimentation rate, antinuclear antibody, angiotensin-converting enzyme, dsDNA, antineutrophil cytoplasmic antibody, perinuclear neutrophil cytoplasmic antibody, and Lyme antibody were all unremarkable. Serum vitamin B12 and folate levels were normal. The patient was diagnosed with possible MS and treated with weekly beta-interferon 1a for 2 years, during which time she had recurrent attacks of uveitis, which were treated with short courses of topical and oral steroids. Chest CT showed no evidence of sarcoidosis.

Due to the unremarkable MRI findings and recurrent episodes of uveitis, we were not convinced the patient had MS. An evaluation was repeated and included testing for serum HTLV-1, which was positive by ELISA. This was confirmed by Western blot, which showed intense immunoreactivity with all antigens, including recombinant gp46-I (env) and gag antigens, thus confirming HTLV-1 infection.[9] Western blot testing for HTLV-2 (ARUP Labs, Salt Lake City, UT) was negative. CSF HTLV-1 was negative initially but repeat testing 1 year later showed intense immunoreactivity by Western blot to all antigens in an identical pattern to that of serum. Of note, though, it has been reported that 20% of patients with spastic paraparesis who are positive for antibodies to HTLV-1 in serum are negative in CSF.[10]

DISCUSSION This case illustrates the challenge in differentiating MS from HTLV-1-associated neurologic disease. Recurrent episodes of vertigo and nystagmus are not uncommon in patients with MS. However, the clinical pearls of this case that suggested a diagnosis different from MS were that the patient did not meet the MRI criteria for either relapsing remitting or primary progressive MS and that the patient had recurrent episodes of uveitis. The patient tested positive for HTLV-1 and in distinction to other cases associated with HTLV-1 infection, this patient lived in the United States and presented with a syndrome characterized by progressive episodes of vertigo and nystagmus, without tremor, dysmetria, or cerebellar atrophy by MRI.[2-5]

Classically, patients infected with HTLV-1 develop HAM/TSP, a slowly progressive myelopathy characterized by spastic paraparesis, hyperreflexia, and early bladder symptoms.[5,6-9] Recent data suggest that clinicians should broaden their definition of HTLV-1-associated neurologic disease.[2,5,9] Specifically, several articles show that a significant proportion of patients develop extraspinal neurologic manifestations, including cerebellar syndromes, optic neuritis, intellectual impairment, and uveitis.[2-5] This has led several authors to suggest changing the name of HAM/TSP to either HTLV-1 neurologic complex or HTLV-1-associated myelo-neuroencephalopathy.[2,5] Our case is congruent with these findings and emphasizes the importance of having a high index of suspicion to test for HTLV-1 in individuals with neurologic illness of unclear etiology.

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