HIV-related neuromuscular diseases: nemaline myopathy, amyotrophic lateral sclerosis and bibrachial amyotrophic diplegia

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The human immunodeficiency virus (HIV) causes diverse disorders of the brain, spinal cord and peripheral nerves. Rarely, polymyositis and myoglobinuria are seen. Two other neuromuscular syndromes in people with HIV antibodies are nemaline myopathy and bibrachial amyotrophic diplegia, a form of motor neuron disease. The associations between these diseases and the possibility that HIV infection could be a risk factor for either amyotrophic lateral sclerosis (ALS) itself or other motor neuron diseases are investigated.

Key words: HIV-Related Neuromuscular Diseases, nemaline myopathy, amyotrophic lateral sclerosis, bibrachial amyotrophic diplegia

Introduction

The human immunodeficiency virus (HIV) causes diverse disorders of the brain, spinal cord and peripheral nerves. Rarely, polymyositis and myoglobinuria are seen. Two other neuromuscular syndromes in people with HIV antibodies are nemaline myopathy and bibrachial amyotrophic diplegia, a form of motor neuron disease. These associations have not been proven epidemiologically and it is uncertain whether HIV infection is a risk factor for either amyotrophic lateral sclerosis (ALS) itself or other motor neuron diseases. However, manifestations of ALS in people with HIV infection can be treated effectively with Highly Active Antiretroviral Therapy (HAART), which would therefore be expected to lower the rate at which new cases appear.

Nemaline Myopathy

History: Drs. Engel and Askanas have been leaders in the study of nemaline myopathy and other conditions in which abnormal inclusions are found in muscle. Nemaline myopathy is defined by the clinical and histologic manifestations. It was named by G. Milton Shy, W. King Engel and their associates in 1963 (1). “Nemaline” was applied because muscle biopsies showed deposits of thread-like structures; the word came from the Greek “nema”. The threads were dark red with the Gomori stain and contain actin. The clinical syndromes are seen most often in infants and children (2, 3). One form, however, occurs in adults, warranting the name “sporadic late onset nemaline myopathy” (SLONM) (4).

In infants and children, the disease is often familial in a pattern consistent with autosomal recessive inheritance. In adults, the disease is almost always sporadic and is seen in association with other conditions (2). Here, we are considering the association of SLONM with HIV infection.

“Sporadic Late-onset Nemaline Myopathy” (SLONM)

Clinical Manifestations: SLONM affects both sexes equally at ages ranging from 20 to 50. The most common clinical syndrome is one of proximal limb weakness of subacute onset and progression, sometimes severe and disabling. The neck extensors may be affected, resulting in the dropped head syndrome. Dysphagia and respiratory failure may appear. Tendon reflexes are usually absent. Fasciculation is not often seen but may be. Sometimes there is evidence of a second muscle disorder, which may be dermatomyositis or polymyositis. Progressive external ophthalmoplegia was reported in two patients (5, 6). The association with HIV was first described by Dalakas and associates (7). It is not clear how often patients with nemaline disease are HIV-positive.

Laboratory Findings: Diagnostic studies are usually indicative of myopathy but sometimes show evidence of denervation. By definition, the muscle biopsy must show
the deposits, which are seen as dark red. At the Mayo Clinic, Chahin et al. (2) examined 3-µm-thick frozen sections stained trichromatically or immunostained for α-actin or myotilin. Electron microscopy in 12 cases identified the rods in all and revealed additional structural abnormalities. CK values were normal or low. Seven of their 14 patients had monoclonal gammopathy and were followed for 1 to 5 years; five died of respiratory failure. Five patients without monoclonal gammopathy were followed for 4 to 23 years and none died of the disease. The presence of gammopathy therefore may be ominous. HIV was excluded in 3 of 6 patients and the other 3 were deemed to have no HIV risk factors.

In other reports, a patient with monoclonal gammopathy had features of both nemaline disease and “trabecular” or “lobulated” muscle fibers as well as bclonal gammopathy (8). Another patient was being treated for dermatomyositis when muscle biopsy showed nemaline rods (9).

Therapy: Immunosuppressive therapy with melphalan, intravenous immunoglobulins (IVIG) or both may be helpful (2, 10-12). Prednisone is sometimes effective (13, 14) but was uniformly ineffective in the Mayo report (2). Autologous stem therapy has also brought benefit (15, 16). Long term immunosuppression with rituximab may be considered. Physical therapy is also indicated to maintain gait and general strength.

**HIV and Motor Neuron Diseases**

In 1985, the fourth year of the emerging AIDS epidemic, Hoffman et al. (17) described a 26 year old man with both upper and lower motor neuron signs. He was still alive a year later. Many feared there would be an epidemic of viral ALS. However, that fear was never realized. By mid-2002, there had been reports of 19 patients with motor neuron disorders, with no evidence that HIV infection increases the likelihood of developing ALS. 13 of the 19 clearly had a disorder that was unlike ALS in one major way, the rapidity of progression. The time from onset of symptoms to severe handicap was measured in weeks and not months, too rapid for conventional ALS. One patient died 3 months after onset (18).

This HIV-related disorder differed in other ways, too. The patients were younger than most cases of motor neuron disease; only 2 of the 13 were older than age 40 while only 10% of all cases of ALS begin before that age. Several of the patients had CSF pleocytosis, unlike ALS. CSF protein content was between 50 and 500 mg/dl in most cases and exceeded 100 mg/dl in two. Two included dementia (19, 20) and one of the 13 had an IgM monoclonal gammopathy (5, 21). Among the 4 patients who came to autopsy, the pathology was more complicated than ALS, with signs of inflammation or vacular myelopathy (22 23).

But the most remarkable difference from ALS was the reversal of symptoms by treatment with nucleosides or HAART (24-26). Some of these patients returned to normal neurologically. However, one patient’s symptoms progressed despite HAART therapy and we have seen one woman whose symptoms started after she had been on therapy for one year.

Therefore ALS in HIV-positive people may take either of two forms, one that responds to HAART and another that does not. The responsive form seems to be related to viral infection. Harbingers of therapeutic response are young age at onset, progression in days or weeks, and abnormal CSF. The unresponsive form may be “ordinary” sporadic ALS that occurs by chance in an HIV-positive person.

A purely upper motor neuron syndrome has also been reported in two HIV-positive patients. One proved to have progressive multifocal leukoencephalopathy (PML) but the other was compatible with primary lateral sclerosis (27). Two other patients had PML (28). A second variation of motor neuron disorder is “brachial amyotrophic diplegia”, which may affect HIV-positive people (29-31) (“man-in-a-barrel syndrome”) and one patient showed lingual fasciculation with hyperreflexia; postmortem examination showed sarcoid brainstem encephalitis (32).

In contrast, one patient had the lower motor neuron syndrome of progressive muscular atrophy (33). One patient with brachial amyotrophy had an SOD1 mutation (34).

Recognition of these HIV-related motor neuron syndromes is important because they may respond to treatment. These syndromes also raise theoretical issues – whether sporadic ALS could ever be caused by a virus or autoimmunity. It is still not known how HIV might cause a motor neuron disorder (35).

**Conclusion**

Both nemaline myopathy and motor neuron disease may be associated with HIV. Treatment of the myopathy with prednisone may or may not be effective but can be tried. HAART may be neurologically effective in HIV patients with ALS. These responses to treatment warrant consideration in planning diagnostic studies.

**References**

1. Shy GM, Engel WK, Somers JE, Wanko T. Nemaline myopathy. A new congenital myopathy. Brain 1963;86:793-810.
2. North K, Ryan MM., Nemaline Myopathy. In: Fagon RA, Bird TD, Dolan CR, et al, eds. Gene Reviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2002 Jun 19 [updated 2010 Oct 21].
3. Ryan MM, Schnell C, Strickland CD, et al. Nemaline myopathy: a clinical study of 143 cases. Ann Neurol 2001;50:312-20.
4. Chahin N, Selcen D, Engel AG. Sporadic-late onset nemaline myopathy. Neurology 2005;65:1158-64.
5. Wright RA, Plant GT, Landon DN, et al. Nemaline myopathy: an unusual cause of ophthalmoparesis. J Neuropathol 1997;56:39-43.
6. Dalakas MC, Pezeshkpour GH, Flaherty M. Progressive nemaline (rod) myopathy responsive to IVIg and immunotherapy. Muscle Nerve 2010;41:272-6.
7. Keller CE, Hays AP, Rowland LP, et al. Adult-onset nemaline myopathy with trabecular muscle fibers. Muscle Nerve 2009;39:871-5.
8. Letournel F, Le Clec'h C, Croué A, et al. Nemaline bodies as unique pathological feature in the course of treated dermatomyositis. Clin Neuropathol 2010;29:357-60.
9. te Sandtis JT, Cumbo-Nacheli G, Dobbie D, et al. HIV-associated nemaline rod myopathy: role of intravenous immunoglobulin therapy in two persons with HIV/AIDS. AIDS Read 2008;18:90-4.
10. de Sanctis JT, Cumbo-Nacheli G, Dobbie D, et al. HIV-associated nemaline rod myopathy with trabecular muscle fibers. Muscle Nerve 2009;39:871-5.
11. Letournel F, Le Clec'h C, Croué A, et al. Nemaline bodies as unique pathological feature in the course of treated dermatomyositis. Clin Neuropathol 2010;29:357-60.
12. Keller CE, Hays AP, Rowland LP, et al. Adult-onset nemaline myopathy with trabecular muscle fibers. Muscle Nerve 2009;39:871-5.
13. de Sanctis JT, Cumbo-Nacheli G, Dobbie D, et al. HIV-associated nemaline rod myopathy: role of intravenous immunoglobulin therapy in two persons with HIV/AIDS. AIDS Read 2008;18:90-4.