Brachial Amyotrophic Diplegia in a Patient With Human Immunodeficiency Virus Infection

Widening the Spectrum of Motor Neuron Diseases Occurring With the Human Immunodeficiency Virus

Joseph R. Berger, MD; Patricio S. Espinosa, MD, MPH; John Kissel, MD

Although amyotrophic lateral sclerosis and progressive spinal muscular atrophy have been recognized to occur in association with human immunodeficiency virus infection, to our knowledge, brachial amyotrophic diplegia, a form of segmental motor neuron disease, has not been previously reported. Brachial amyotrophic diplegia results in severe lower motor neuron weakness and atrophy of the upper extremities in the absence of bulbar or lower extremity involvement, pyramidal features, bowel and bladder incontinence, and sensory loss. We describe a human immunodeficiency virus–seropositive man without severe immunosuppression or prior AIDS-defining illnesses who had brachial amyotrophic diplegia. This disorder may represent one end of a spectrum of motor neuron diseases occurring with this retrovirus infection.

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Motor neuron disease associated with human immunodeficiency virus (HIV) infection was first reported in 1985, 4 years after the initial description of AIDS. Clinical patterns of HIV-associated motor neuron disease may mirror those of amyotrophic lateral sclerosis (ALS) or progressive spinal muscular atrophy (PSMA). However, to our knowledge, a segmental form of PSMA referred to as brachial amyotrophic diplegia (BAD) has not been previously described in association with HIV infection. This disorder is a form of neurogenic “man-in-the-barrel” syndrome in which severe bilateral upper extremity weakness is unaccompanied by bulbar lower extremity or pyramidal abnormalities. When associated with motor neuron disease, it has also been referred to as the flail arm syndrome and the hanging arm syndrome. BAD is classified as a form of segmental lower motor neuron disease. While a similar clinical phenotype of bilateral upper extremity weakness may occur following cerebral, brainstem, and cervical spinal cord, these may be distinguished from BAD by clinical presentation and radiographic and electrophysiological studies. Furthermore, the lack of involvement of bulbar and lower extremity muscles, the absence of pyramidal signs, and the long survival with this disorder distinguish it from ALS. We describe an HIV-seropositive man presenting with progressive upper extremity weakness that developed in the absence of a detectable viral load or any preceding AIDS-related complications.

REPORT OF A CASE

This 35-year-old man was first aware of a slowly progressive weakness of the right shoulder in June 2000 when he noted difficulty lifting heavy objects above his head with his right arm. The symptoms in his right arm progressed, and by June 2001, a similar weakness had developed in the left shoulder. Weakness and wasting were progressive in both upper extremities and in his chest muscles in the ensuing months. He denied speech or swallowing difficulties, leg weakness, sphincter distur-
A physical examination performed in April 2003 showed a slender man, weighing 55.8 kg. His cognition, language, and speech were normal. The result of a cranial nerve examination was normal. There was dramatic wasting of the muscles of the shoulder girdle and upper extremity and to a lesser extent the muscles of the forearms, hands, chest, and thorax (Figure). The scapulae were winged. Coarse fasciculations were observed in multiple muscles in the upper extremity and over the chest. His abdominal muscles were preserved. No spasticity was evident. Upper extremity strength was graded as trace in both deltoids, 2 of 5 in the right biceps and brachioradialis, 3 of 5 in the left biceps and brachioradialis, 4 of 5 in both triceps, and 4 of 5 at the wrist extensors and flexors, although the extensors were weaker. His interossei and other intrinsic hand muscles were mildly weak. Wasting in the lower extremities was confined to both extensor digitorum brevis muscles, greater on the left, which was associated with weakness of toe extension. Otherwise, strength in his lower extremities was preserved. Muscle stretch reflexes were graded as absent at the right biceps and brachioradialis, +1 at the right triceps, trace at the left biceps and brachioradialis, +1 at the left triceps, +2 at both knee jerks, and trace at the ankles. There was no Hoffmann or Babinski sign, and his jaw jerk was normal. His gait was normal. Pinprick and temperature sensation were diminished to the lower third of the calves. Vibratory and position sense was diminished in a stocking distribution in the distal lower extremities, and the Romberg sign was positive.

The result of magnetic resonance imaging of the cervical spine was normal, with minimal degenerative changes of the spine. With the exception of a mildly increased creatine kinase level (3.86 × 10³ U/L), the results of hematologic and other laboratory studies, including erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibody, tests for hereditary neuropathy with liability to pressure palsies, and antibodies to GM1 and myelin-associated glycoprotein, were negative or normal. The complete blood cell count revealed a hemoglobin level of 12.3 g/dL, a hematocrit of 36%, and a white blood cell count of 6500/µL, with a normal differential. The vitamin B₁₂ level was 528 pg/mL (390 pmol/L). Cerebrospinal fluid analysis showed 3/µL leukocytes, 0 erythrocytes, a glucose level of 115 mg/dL (6.38 mmol/L), a protein level of 5.5 × 10⁻² g/dL, negative microbiological study results, including those for the VDRL test and cryptococcal antigen, normal cytologic test results, a normal IgG index, and 7 oligoclonal bands (attributed to HIV infection). Cerebrospinal fluid HIV viral assays were not performed. Electrophysiologic studies performed on February 20, 2001, showed evidence of active and chronic denervation bilaterally of muscles innervated by C5 through the middle thoracic nerve roots by electromyography. The result of needle electromyography of the lower extremities was normal, with the exception of the observation of long-duration large-amplitude motor unit action potentials, fibrillation potentials, and mildly reduced recruitment in the muscles supplied by the superficial and deep peroneal nerves. Nerve conduction studies in the legs revealed sensory amplitudes all greater than 60% of the lower limit of normal for our laboratory, with preserved conduction velocities. Motor conduction velocities were all greater than the 90th percentile of the lower limit of normal, with normal amplitudes. The changes overall were compatible with a mild to moderate distal sensorimotor polyneuropathy with predominantly axonal features. The findings on the nerve conduction study were complex and believed to be most consistent with diabetic peripheral neuropathy, a right peroneal neuropathy, and bilateral mild ulnar nerve entrapments at the elbow.

A trial of intravenous immunoglobulin was initiated in October 2003 without any improvement. Through January 2004, there was neither significant progression of his weakness nor development of any cranial nerve abnormalities or weakness, cramps, or fasciculations of the lower extremities.

**COMMENT**

Motor neuron disease with HIV infection may appear in several forms. A summary of previously reported cases of motor neuron disease complicating HIV infection and a summary of our patient are included in the Table. Motor neuron disease with HIV infection may be indistinguishable from classic ALS, resulting in an inexorably progressive disorder of upper and lower extremities.
<table>
<thead>
<tr>
<th>Source</th>
<th>Age, y/ Sex</th>
<th>Clinical Manifestations</th>
<th>CD4 Cell Count/µL</th>
<th>Viral Load at Dx</th>
<th>CSF Findings</th>
<th>Opportunistic Illness</th>
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<tbody>
<tr>
<td>Zoccol et al.5, 2002</td>
<td>44/M</td>
<td>CC: hand weakness, cramps, and weight loss. NE: hypotrophy and fasciculations (tongue and upper and lower limbs); no sensory abnormalities; Hoffman and Babinski signs present.</td>
<td>360</td>
<td>34 000 copies/mL</td>
<td>Leukocytes, 7/µL; glucose, 43 mg/dL; protein, 6.1 × 10² g/dL; HIV RNA, 370 copies/mL</td>
<td>None</td>
<td>Zidovudine, lamivudine, and nevirapine</td>
<td>Bedridden, respiratory failure, death</td>
<td>3 y</td>
</tr>
<tr>
<td>Nishio et al.6, 2001</td>
<td>42/F</td>
<td>CC: dysphagia, dysarthria, and dysphonia. NE: hypotrophy and fasciculations (tongue) and proximal limb weakness and atrophy; no sensory abnormalities.</td>
<td>107</td>
<td>44 510 copies/mL</td>
<td>Leukocytes, 29/µL; glucose, 46 mg/dL; protein, 12.6 × 10² g/dL</td>
<td>None</td>
<td>Stavudine, lamivudine, and nevirapine mesylate</td>
<td>Improvement of the symptoms after therapy, alive</td>
<td>Alive, minimal neurological problems?</td>
</tr>
<tr>
<td>Verma et al.9, 1990</td>
<td>32/M</td>
<td>CC: progressive lower limb weakness plus cramps. NE: upper and lower limb proximal weakness and fasciculations; mild atrophy; no sensory abnormalities.</td>
<td>NA (T4/T8, 0.73)</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
<td>NA</td>
<td>Successive opportunistic infections, death</td>
<td>2 y</td>
</tr>
<tr>
<td>Casado et al.4, 1997</td>
<td>30/M</td>
<td>CC: progressive upper limb weakness plus hypotrophy. NE: upper and lower limb distal weakness and fasciculations; mild atrophy; no sensory abnormalities.</td>
<td>NA (T4/T8, 0.76)</td>
<td>NA</td>
<td>Normal</td>
<td>None</td>
<td>NA</td>
<td>Deterioration of PSMA Sx, HIV infection, stable</td>
<td>Alive at publication</td>
</tr>
<tr>
<td>Galassi et al.7, 1998</td>
<td>30/M</td>
<td>CC: extremity weakness, cramps, weight loss, and fatigue. NE: proximal limb asymmetric weakness; flexor plantar response; mild atrophy; no sensory abnormalities.</td>
<td>340 (T4/T8, 0.4)</td>
<td>NA</td>
<td>Leukocytes, 0/µL; glucose, 17.4 × 10² g/dL; protein, 60 mg/dL</td>
<td>Skin bacterial infections</td>
<td>Zidovudine, zalcitabine, and methylprednisolone</td>
<td>Progressive respiratory failure, death</td>
<td>NA</td>
</tr>
<tr>
<td>Sastre-Garriga et al.8, 2000</td>
<td>39/F</td>
<td>CC: lower limb weakness and cramps. NE: hypotrophy and fasciculations (tongue); distal limb weakness; no sensory abnormalities.</td>
<td>540</td>
<td>NA</td>
<td>Leukocytes, 0/µL; glucose, 60 mg/dL; protein, 2 × 10² g/dL</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<th>Source</th>
<th>Age, y/ Sex</th>
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<th>Treatment</th>
<th>Outcome</th>
<th>Survival</th>
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</thead>
<tbody>
<tr>
<td>MacGowan et al.2 2001</td>
<td>32/F</td>
<td>CC: generalized weakness, weight loss, and dysarthria. NE: tongue fasciculations and upper and lower limb proximal and more distal weakness; Hoffman and plantar signs present; no sensory abnormalities.</td>
<td>44</td>
<td>77 900 copies/mL</td>
<td>Leukocytes, 14/µL; glucose, NA; protein, 13.4 × 10^2 g/dL</td>
<td>None</td>
<td>Zidovudine, lamivudine, and nevirapine</td>
<td>Deterioration; and after antiretroviral treatment, full recovery</td>
<td>Alive</td>
</tr>
<tr>
<td>Goldstein et al.3,1993</td>
<td>22/F</td>
<td>CC: lower extremity pain and weakness. NE: upper limb P/D, 4/5; distal limb P, 3/5, D 2/5; mild sensory abnormalities.</td>
<td>438 (T4/T8, 0.39)</td>
<td>Leukocytes, 1/µL; glucose, NA; protein, 7.3 × 10^2 g/dL</td>
<td>None</td>
<td>Zidovudine, IV immunoglobulin, and methylprednisolone</td>
<td>Deterioration, relapses, improvement</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38/M</td>
<td>CC: facial droop and upper limb weakness. NE: upper and lower weakness; DTR absent; no sensory abnormalities.</td>
<td>353 (T4/T8, 0.45)</td>
<td>Leukocytes, 16/µL; glucose, NA; protein, 15 × 10^2 g/dL</td>
<td>None</td>
<td>IV immunoglobulin, methylprednisolone, and plasmapheresis</td>
<td>Deterioration, stabilization</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Huang et al.10, 1993</td>
<td>45/M</td>
<td>CC: generalized weakness, fasciculations, weight loss, and quadriplegia. NE: tongue atrophy and fasciculations; upper and lower limb paralysis; no sensory abnormalities.</td>
<td>397 (T4/T8, NA 1.13)</td>
<td>Leukocytes, 11/µL; glucose, 60 mg/dL; protein, 5.7 × 10^2 g/dL</td>
<td>None</td>
<td>Zidovudine</td>
<td>No further deterioration</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Moulignier et al.7 2001</td>
<td>27/M</td>
<td>CC: right hand weakness, muscle wasting, and dysarthria.</td>
<td>84</td>
<td>NA</td>
<td>Leukocytes, 5/µL; protein, 4.6 × 10^3 g/dL</td>
<td>None</td>
<td>Zidovudine</td>
<td>Transient stabilization 6 mo (ADC)</td>
<td>6 mo (ADC)</td>
</tr>
<tr>
<td></td>
<td>61/M</td>
<td>CC: left leg weakness, muscle wasting, and cramps.</td>
<td>44</td>
<td>NA</td>
<td>Leukocytes, 8/µL; protein, 5.4 × 10^2 g/dL</td>
<td>None</td>
<td>Zidovudine</td>
<td>Full recovery 2 y (OI)</td>
<td>2 y (OI)</td>
</tr>
<tr>
<td></td>
<td>29/M</td>
<td>CC: left leg weakness and tongue fasciculations.</td>
<td>2</td>
<td>NA</td>
<td>Leukocytes, 3/µL; protein, 2.5 × 10^2 g/dL</td>
<td>None</td>
<td>Zidovudine</td>
<td>Partial recovery Unknown (unavailable for follow-up) 3 y (OI)</td>
<td>Unknown (unavailable for follow-up) 3 y (OI)</td>
</tr>
<tr>
<td></td>
<td>22/M</td>
<td>CC: bilateral lower limb weakness, muscle wasting, and fasciculations.</td>
<td>37</td>
<td>3.7 log^10 copies/mL</td>
<td>Leukocytes, 13/µL; protein, 5.2 × 10^2 g/dL</td>
<td>None</td>
<td>Zidovudine and didanosine</td>
<td>Partial recovery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25/M</td>
<td>CC: left arm weakness, muscle wasting, and fasciculations.</td>
<td>123</td>
<td>4.9 log^10 copies/mL</td>
<td>Leukocytes, 2/µL; protein, 3.6 × 10^2 g/dL</td>
<td>None</td>
<td>Zidovudine and zalcitabine</td>
<td>Partial recovery 4 y (ADC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40/F</td>
<td>CC: left arm weakness and mild muscle atrophy.</td>
<td>227</td>
<td>3.3 log^10 copies/mL</td>
<td>Leukocytes, 1/µL; protein, 4.2 × 10^2 g/dL</td>
<td>None</td>
<td>Zidovudine and didanosine</td>
<td>Full recovery Alive for &gt;3 y</td>
<td></td>
</tr>
</tbody>
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(continued)
motor neurons. Alternatively, progressive lower motor neuron disease affecting bulbar and extremity muscles may occur in the absence of upper motor neuron findings consistent with PSMA. Other disorders occurring with HIV infection that mimic motor neuron disease include chronic inflammatory polyradiculoneuropathy, axonal motor polyradiculoneuropathy, and multifocal motor neuropathy with anti-GM1 antibodies. While progressive lower motor neuron weakness is seen with these disorders, the slow tempo of our patient's illness would be distinctly unusual for chronic inflammatory polyradiculoneuropathy and multifocal motor neuropathy, and its severity and distribution inconsistent with HIV-associated axonal motor polyradiculoneuropathy.

Our patient had focal weakness of the right upper extremity that progressed to involve the left upper extremity during the ensuing year. The weakness and wasting have remained confined to a few myotomes of the cervical and upper thoracic region. There has been neither involvement of bulbar muscles nor progressive weakness of his lower extremities. The lower extremity findings of distal sensory loss, depressed ankle jerks, and distal wasting and weakness are the consequence of his concomitant diabetic peripheral neuropathy and mild entrapment neuropathies. Therefore, we believe that profound weakness and wasting of his upper extremities are consistent with BAD.

Diabetes may result in brachial and lumbosacral plexopathies, resulting in a disorder referred to as diabetic radiculoplexus neuropathy (or diabetic amyotrophy) that may mimic the disorder observed in our patient. This disorder, however, affects the lumbosacral plexus in most cases, and upper extremity involvement is uncommon. In addition, patients with brachial diabetic radiculoplexus neuropathy typically have unilateral weakness that progresses more rapidly than in our patient with preceding weight loss, severe pain, and sensory and autonomic abnormalities. Because none of these features was present in our patient, we think this an unlikely cause of our patient's disorder.

Motor neuron disease occurring in association with HIV infection has been attributed to direct damage to the motor neurons by HIV, neurotoxic HIV viral proteins, cytokines and chemokines arising consequent to HIV infection, and opportunistic viruses that directly attack motor neurons. The prototypical virally mediated motor neuron disease is poliomyelitis; however, it is clinically quite distinct from the inherited and idiopathic forms of motor neuron disease. Flaccid paralysis has been reported with various viruses in the Enterovirus genus. Recently, French investigators have found the nucleic acid of enteric cytopathogenic human orphan virus, an enterovirus, in the neuronal cell bodies within the gray matter of the spinal cord of 88% of patients with ALS, suggesting a possible association between this enterovirus and ALS. However, poliovirus and other enteroviruses, when associated with weakness, are typically characterized by an acute febrile illness followed by a flaccid paralysis of 1 or more limbs. Whether HIV infection it-

### Table. Summary of Cases of Motor Neuron Disease Heralding HIV Infection (cont)

<table>
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<tr>
<th>Source</th>
<th>Age, y/</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Hoffman et al, 1985</td>
<td>26/M</td>
<td></td>
<td>CC: weakness, atrophy, and fasciculations of the left arm.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
<td>NA</td>
<td>Progressive</td>
<td>1 y</td>
</tr>
<tr>
<td>Sher et al, 1988</td>
<td>30/M</td>
<td></td>
<td>CC: weakness, wasting, and fasciculations.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
<td>NA</td>
<td>Partial recovery</td>
<td>3 mo (pneumonia)</td>
</tr>
<tr>
<td>Simpson et al, 1994</td>
<td>45/M</td>
<td></td>
<td>CC: asymmetric limb weakness, atrophy, and fasciculations.</td>
<td>560</td>
<td>NA</td>
<td>NA</td>
<td>Zidovudine, prednisone, and IV immunoglobulin</td>
<td>Stabilization</td>
<td>24 mo (opportunistic infections)</td>
<td>Alive 46 mo after onset</td>
</tr>
<tr>
<td>Present case</td>
<td>35/M</td>
<td></td>
<td>CC: weakness (upper extremities). NE: atrophy of shoulder girdle, upper proximal extremities, and pectoral and thoracic muscles; mild sensory abnormalities due to concomitant diabetic neuropathy.</td>
<td>244</td>
<td>Undetectable viral load</td>
<td>Leukocytes, 3/µL; glucose, 115 mg/dL; protein, 5.5 × 10^4 g/dL; oligoclonal bands, 7</td>
<td>None</td>
<td>Zidovudine, didanosine, abacavir succinate, and IV immunoglobulin</td>
<td>Stabilization</td>
<td>no further deterioration</td>
</tr>
</tbody>
</table>

Abbreviations: ADC, AIDS dementia complex; CC, chief complaint; CSF, cerebrospinal fluid; D, distal; DTR, deep tendon reflex; Dx, diagnosis; HIV, human immunodeficiency virus; IV, intravenous; NA, data not available; NE, neurological; OI, osteogenesis imperfecta; P, proximal; PSMA, progressive spinal muscular atrophy; SX, symptoms; T4/T8, ratio of CD4 to CD8 lymphocytes.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.05551.
self or an accompanying, currently unrecognized, opportunistic infection is responsible for the motor neuron findings in HIV-infected persons with motor neuron disease or whether it is unrelated to HIV infection remains to be determined. Findings of reverse transcriptase, 38 antibodies directed to human retroviral antigens, 39 an association of human T-lymphotropic virus I with clinical and pathological features consistent with ALS, 40-41 amplification of human T-lymphotropic virus tax/rev, 39 animal models of retrovirus-induced motor neuron disease, 42,43 and the presence of PSMA and ALS in HIV infection suggest that HIV infection is causative or contributory. While the pathogenesis of ALS remains a conundrum, several theories have been proposed. Among the possible mechanisms that are considered are neuronal excitation and free radical generation. 44 Both of these mechanisms have also been proposed as pathways to brain neuronal injury in the setting of HIV infection. 45 Mitochondria, through several mechanisms, have also been suggested as instrumental in ALS, as in other neurodegenerative disorders. 46 A critical role of the mitochondria in neuronal apoptosis has been suggested with neurotoxic HIV proteins, gp120, 47 and Tat. 48 Some investigators have also advanced a role for autoimmunity in ALS. 49,50 Antineuronal antibodies have been demonstrated in HIV infection, and may correlate with the presence of dementia. 51,52 Therefore, several proposed pathogenetic mechanisms for ALS may also be operative in HIV-associated central nervous system disease. In conclusion, motor neuron disease occurs in association with HIV infection. The spectrum of HIV-associated motor neuron disease is broad and includes BAD, PSMA, and ALS. These disorders remain rare, and their underlying pathogenesis is uncertain.

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Author Contributions: Study concept and design: Berger and Kissel. Acquisition of data: Berger and Kissel. Analysis and interpretation of data: Berger and Espinosa. Drafting of the manuscript: Berger and Espinosa. Critical revision of the manuscript for important intellectual content: Berger and Kissel. Administrative, technical, and material support: Berger and Espinosa. Study supervision: Berger.

REFERENCES


