An 8-Year-Old Boy With Ascending Paralysis

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CASE PRESENTATION

Presentation

A previously healthy 8-year-old boy presented in February with 7 days of fever, lethargy, and progressive ascending weakness. He had no animal, insect, travel, or unusual dietary exposures and was living with 4 siblings and 2 parents (all healthy) in the central United States.

The patient was fatigued but not distressed. Temperature was 99.3°F; pulse, 89 beats/minute; respiratory rate, 20 breaths/minute; blood pressure, 115/67 mm Hg; and oxygen saturation, 92%. On examination, he answered questions appropriately with 1 word dyspnea. Cardiac, respiratory, and abdominal exams were otherwise unremarkable. He had no lymphadenopathy. He had 0/5 strength and areflexia in the upper and lower extremities, urinary retention, and complete loss of sensation below spinal level C3–4.

Laboratory evaluation revealed a peripheral white blood cell (WBC) count of 3.4 × 10^3 cells/μL (reference range, 5.8–10.3 × 10^3 cells/μL), including 67% segmented forms, 23% lymphocytes, and 5% reactive lymphocytes. C-reactive protein was <0.5 mg/dL (range, 0–1 mg/dL). Serum chemistries, transaminases, and ammonia were within normal limits. Cerebrospinal fluid (CSF) analysis showed 73 WBC/mL (range, 0–5 cells/mL), including 88% lymphocytes and 8% neutrophils; 96 red blood cells (RBC)/mL (range, 0–5 cells/mL); protein of 382 mg/dL (range, 12–60 mg/dL); and glucose of 35 mg/dL (range, 40–75 mg/dL). Bronchoalveolar lavage had negative polymerase chain reaction (PCR) testing for Mycoplasma pneumoniae and 14 respiratory viruses as well as negative culture for bacteria, herpes simplex virus (HSV), and cytomegalovirus. Additional PCR testing for enterovirus (throat, rectum, CSF), HSV (CSF), and respiratory viruses (nasal wash) was negative. Epstein-Barr virus serology was positive for immunoglobulin G (IgG) to viral capsid antigen and Epstein-Barr nuclear antigen, consistent with past infection. Brain and spinal magnetic resonance imaging (MRI) revealed multifocal areas of nonenhancing T2 hyperintensity involving the supratentorial white matter and brainstem, diffuse central spinal cord T2 hyperintensity without enhancement from the brainstem to T11, and cervical spinal cord swelling from C2–C7 (Figure 1A–C). These findings were believed to be consistent with an infectious or inflammatory demyelinating process. Anti-neuromyelitis optica (NMO) IgG testing was negative.

Clinical Course

The patient was diagnosed with acute demyelinating encephalomyelitis (ADEM) with multiple-segment transverse myelitis. He was treated with corticosteroids, plasma exchange, and intravenous Ig (IVIG). He required tracheostomy and gastrostomy tubes, which were removed before discharge. Near the end of his 3-month hospitalization, repeat MRI revealed resolution of brain lesions but new spinal cord enhancement; ADEM was still considered the likely diagnosis, and he was given 2 additional doses of IVIG. At discharge, he remained paraplegic.

Six months after presentation, the patient developed decreased visual acuity and eye pain, consistent with bilateral optic neuritis. A complete blood count demonstrated continued, mild leukopenia, with a WBC count of 5.3 × 10^3 cells/μL (39% segmented forms, 46% lymphocytes, and 7% eosinophils). Cerebrospinal fluid revealed 12 WBC/mL (92% neutrophils, 6% monocytes), 29 RBC/mL, protein of 98 mg/dL, and glucose of 37 mg/dL. Magnetic
resonance imaging showed no optic nerve enhancement, but it did reveal continued T2 enhancement of the central cord and new enhancement along the ventral cord from T5–T9. Chest computed tomography demonstrated prominent axillary lymph nodes, left greater than right, that were not palpable on exam; biopsy revealed reactive follicular hyperplasia. Repeat anti-NMO IgG testing was negative; however, based on clinical criteria, the patient was diagnosed with NMO, treated with a second course of corticosteroids and plasma exchange, and started on rituximab to decrease the risk of relapse. Visual acuity improved over several weeks.

The patient sought a second opinion 7 months after presentation, and a laboratory test revealed the underlying diagnosis.

DISCUSSION

Diagnosis

A variety of infectious etiologies are associated with demyelinating disorders. In addition to those previously tested, the consulting team considered West Nile virus, human immunodeficiency virus (HIV), human T lymphotropic virus-1, enterovirus 71, and Lyme disease. Enzyme-linked immunosorbent assay (ELISA) and Western blot testing for HIV were positive, and plasma quantitative HIV RNA PCR demonstrated 43,000 viral copies/mL. The CD4 count was normal at diagnosis. Frozen specimens from the patient’s initial presentation (month 0) revealed high plasma and CSF viral loads and incomplete seroconversion (positive ELISA and negative Western blot), consistent with primary HIV infection (Table 1). Detailed questioning did not identify known needle stick injury, exposure to blood products before presentation, sexual abuse or activity, or traumatic blood exposure. The child’s parents and all 4 siblings were tested and were negative for HIV infection by serology and plasma DNA PCR. Public health department and forensics evaluations have not revealed a source of infection, which is exceptionally uncommon based on our own experience and a review of the literature.

The patient was started on highly active antiretroviral therapy (HAART) 7 months after initial presentation,
which included zidovudine, emtricitabine, and lopinavir/ritonavir. This regimen was chosen to maximize central nervous system penetration and minimize neural toxicity, pill burden, and potential drug interactions with other chronic medications. He continues to receive rituximab every 6 months to prevent relapse of NMO. Since starting HAART and rituximab at month 7, his plasma HIV viral load has become undetectable. He has not had any neurologic recovery, nor has he had neurologic relapses over a period of 16 months. Magnetic resonance images, obtained at 17 months after symptom onset, showed diffuse volume loss of the lower thoracic spinal cord (Figure 1D).

**Teaching Points**

Infection with HIV may be associated with a number of neurologic manifestations. With primary infection, acute retroviral syndrome may include headache, retro-orbital pain, aseptic meningitis, and transient encephalopathy [1]. Symptoms usually resolve over days to weeks. With immunosuppression associated with chronic HIV infection, numerous complications may produce neurologic symptoms, including HIV encephalopathy, progressive multifocal leukoencephalopathy secondary to John Cunningham virus infection, cytomegalovirus encephalitis, and mass-associated lesions such as lymphoma and toxoplasmosis. Chronic HIV infection can also lead to a spectrum of neurocognitive deficits, from mild cognitive defects to debilitating encephalopathy. Highly active antiretroviral therapy is known to significantly limit these complications.

Demyelination disorders are increasingly recognized as a significant but uncommon cause of neurologic disease in children [2]. Often associated with or after infection, symptoms may range from mild to severe, with a variety of manifestations. Although demyelination disorders such as ADEM, transverse myelitis, optic neuritis, NMO, and a multiple sclerosis (MS)-like syndrome have been associated with primary and chronic HIV infection in adults, these syndromes have rarely been reported in association with HIV infection in children [3–9]. To our knowledge, this patient represents the 6th reported case of HIV-associated NMO and the first ever case reported in a child [4, 6, 8, 9]. Of the 6 cases, 4 (67%) had known pre-existing HIV-infection and 2 (33%) were on HAART; both new HIV diagnoses were associated with plasma viral loads greater than 500 000 copies/mL on presentation, and 1 of these patients showed significant improvement when treated with HAART and systemic steroids [8]. In a recent review of 16 adults with HIV-associated demyelinating disease (11 MS-like, 4 NMO, 1 ADEM), common features also seen in our patient included relapsing disease (75%), bilateral optic neuritis (69%), thoracic transverse myelitis (63%), and loss of bowel/bladder function (56%) [9]. There do not appear to be any distinguishing features of HIV-associated NMO compared with non-HIV-associated NMO, although some evidence suggests HAART initiation may be effective in adults with HIV-associated MS-like disease [9].

Neuromyelitis optica is thought to be caused by immune dysregulation in a genetically susceptible host [2, 10]. A diagnosis of antibody-negative NMO requires transverse myelitis, optic neuritis, and 2 of the following: transverse myelitis extending beyond 3 spinal cord levels, MRI not compatible with MS, and presence of anti-NMO IgG [2, 10]. Clinically, patients can present with recurrent or simultaneous episodes of optic neuritis and transverse myelitis. Cerebral symptoms including encephalopathy occur in 45% of individuals. In 90% of clinical NMO cases, an autoantibody (anti-NMO IgG) that binds to the aquaporin-4 water channel in brain, optic nerves, and spinal tissue is present and thought to be pathogenic. There is a subpopulation of patients with clinical NMO that never develops detectable anti-NMO antibodies. Relapsing disease in NMO occurs in 53%–100% of patients. Relapsing disease helps distinguish NMO from ADEM, which is typically a monophasic illness. The presence of multiple segment (>3) transverse myelitis distinguishes NMO from MS.

Table 1. Laboratory Testing for Human Immunodeficiency Virus (HIV)

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Month 0*</th>
<th>Month 7†</th>
<th>Month 8</th>
<th>Month 9</th>
<th>Month 10</th>
<th>Month 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA PCR copies/mL (plasma)</td>
<td>&gt;10 million</td>
<td>43 000</td>
<td>23 000</td>
<td>18 10</td>
<td>510</td>
<td>—</td>
</tr>
<tr>
<td>HIV RNA PCR copies/mL (CSF)</td>
<td>467 000</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>HIV DNA PCR</td>
<td>Reactive</td>
<td>Reactive</td>
<td>Reactive</td>
<td>Reactive</td>
<td>Reactive</td>
<td>Reactive</td>
</tr>
<tr>
<td>HIV ELISA</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>HIV Western blot</td>
<td>1134 (37%)</td>
<td>604 (30%)</td>
<td>815 (48%)</td>
<td>815 (48%)</td>
<td>815 (48%)</td>
<td>815 (48%)</td>
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<td>CD4 count, absolute (%)</td>
<td></td>
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Abbreviations: CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; PCR, polymerase chain reaction.

*Presentation with acute neurologic disease.
†Second opinion during which underlying diagnosis was made.
oral taper [2, 10, 11]. Patients with severe, acute neurologic deficits are also often treated with plasma exchange. Medications used to prevent relapse include rituximab, mycophenolate, and azathioprine. Neuromyelitis optica is associated with long-term neurologic deficits in 90% of cases, including 54% with visual and 44% with motor deficits. In the absence of specific treatment guidelines for HIV-associated NMO, we continued rituximab and reasoned that the addition of HAART would reduce a potential trigger of further inflammation and limit his risk of developing permanent blindness.

**CONCLUSIONS**

This case highlights that HIV infection may be a trigger for demyelination and other neurologic disorders in children. Testing for HIV infection should be considered in patients with unexplained neurologic presentations, even in the absence of known exposures.

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

**References**