Human T-lymphotropic Virus Type-I (HTLV-I)-associated Myelopathy with Bulbar Palsy-type Amyotrophic Lateral Sclerosis-like Symptoms

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Abstract

We herein report a case of Human T-lymphotropic virus type-I (HTLV-I)-associated myelopathy with bulbar palsy-type amyotrophic lateral sclerosis-like symptoms. A 52-year-old woman developed dyslalia at approximately 40 years of age, which slowly progressed. She presented with muscular atrophy and increased tendon reflexes of the extremities as well as bulbar palsy, from which motor neuron disease was suspected. Cerebrospinal fluid (CSF) testing revealed no abnormalities except for an elevated neopterin concentration at 143.17 pmol/mL (normal ≤30 pmol/mL). Her serum and CSF anti-HTLV-I antibody titers were also high. Intravenous infusions of methylprednisolone decreased the CSF neopterin concentration to 50.33 pmol/mL. Subsequent oral prednisolone therapy was effective in alleviating the symptoms.

Key words: HTLV-I-associated myelopathy (HAM), bulbar palsy, amyotrophic lateral sclerosis (ALS), neopterin, anti-HTLV-I antibody, steroid therapy


Introduction

Human T-lymphotropic virus type-I (HTLV-I)-associated myelopathy (HAM) is a slowly progressive myelopathy caused by one of the human retroviruses, HTLV-I. The principal clinical manifestations of HAM are spastic paraplegia and pollakiuria (1). Cerebrospinal fluid (CSF) testing in HAM patients shows high levels of anti-HTLV-I antibody titer and neopterin (2). Immunotherapies including steroids and interferon-alpha are applied for the treatment of HAM. We herein report a case of HAM with bulbar palsy, muscular atrophy, and weakness of the upper limbs and trunk that required differentiation from bulbar palsy-type amyotrophic lateral sclerosis (ALS).

Case Report

A 52-year-old woman presented with the main complaint of dyslalia and gait disturbance. She had no remarkable medical history and did not smoke or drink alcohol. Her mother had suffered from dyslalia that developed in her 40s and she died at 70 years of age.

The patient developed dyslalia at approximately 40 years of age, which slowly progressed. Aspiration occurred at approximately 50 years of age. She visited our clinic due to frequent falls on level ground. She presented with muscular atrophy and increased tendon reflexes of the extremities as well as bulbar palsy. Because her deceased mother reportedly had similar symptoms, familial ALS was suspected and she was admitted to hospital for further evaluation.

On admission, the patient’s height was 161 cm and body weight was 38.6 kg. Her vital signs were normal. She was alert and had normal cognitive function. The patient’s facial muscle strength was slightly reduced in the upper part and moderately reduced in the lower part. She also had symptoms of cranial nerve disorder which included constant mouth opening, forced crying, dysphagia, dyslalia, a loss of gag reflex, tongue atrophy, fasciculation, and poor tongue protrusion. There were no other abnormal symptoms in the...
cranial nerve system. Her extremities were spastic, and systemic muscular atrophy and fasciculation were observed. A manual muscle test revealed muscle weakness, predominantly in the proximal muscles, and was graded a 4 out of 5. The jaw reflex and tendon reflexes of the extremities were hyperactive. Babinski reflex was bilaterally positive and the patient had a spastic gait. Her autonomic symptoms included constipation and micturition frequency at approximately 8 to 10 times daily. She had no coordination disturbance or sensory disturbance.

Blood tests showed no significantly abnormal values in the patient’s blood cell counts, blood biochemistry, markers of the auto-immune system, or various tumor markers. General CSF testing revealed no abnormal results. Magnetic resonance imaging scans of the brain and spinal cord revealed no abnormal findings. Nerve conduction studies also showed normal results. Needle electromyography showed acute neurogenic changes in the first dorsal interosseous muscle in the hand and anterior tibial muscle. SOD1 mutations were not identified in the genetic testing.

On admission, a presumptive diagnosis of familial ALS was made due to the patient’s family history, the involvement of the upper and lower motor neurons in the brain stem (and upper and lower extremities), as well as a lack of sensory disturbance. However, the CSF neopterin concentration obtained on admission was elevated at 143.17 pmol/mL (normal concentrations ≤30 pmol/mL) (2) which was suggestive of an immune-mediated abnormality of the central nervous system. Therefore, testing for HTLV-I infection was conducted. The patient’s serum and CSF anti-HTLV-I antibody titers were elevated (1:51,200 in serum and 1:128 in CSF). The HTLV-I proviral DNA load in the peripheral blood was high at 498 copies/μl (the mean±SD of HTLV-1 proviral load in asymptomatic HTLV-I carriers is 120±17 copies/10^5 PBMCs (5)). We diagnosed this case as having HAM for the following reasons: 1) the titer of anti-HTLV-I antibody (1:128) in CSF was too high as a HTLV-I carrier with the other neurological disorders and 2) the 498 copies of HTLV-I proviral load was excessively high as a HTLV-I carrier. Matsuzaki et al. reported that ALS-like HAM patients with high HTLV-I proviral loads respond well to steroid therapy (4). Therefore, steroid therapy with intravenous infusions of methylprednisolone (1,000 mg/day) for 3 days was started and the CSF neopterin concentration rapidly fell to 50.33 pmol/mL after treatment. Subsequently, therapy with oral prednisolone was initiated at a dose of 15 mg daily. Although the dyslalia still persisted, it has improved moderately. The patient’s grip strength (kg) improved from 12/13 (right/left hand) to 14/18. Her micturition frequency has reduced from approximately ten times daily to six times daily. Although amelioration of the gait disturbance has not been observed, the frequency of falls has decreased. After discharge, the dose of prednisolone was tapered. At a dose of 5 mg daily, micturition frequency increased and the CSF neopterin concentration rose to 194 pmol/mL. Hence, the dose of prednisolone was increased to 10 mg daily. Thereafter, the patient’s symptoms remained stable without deterioration. 

### Discussion

There are several reports of HAM presenting with ALS-like symptoms as was seen in our case. In one case HAM was diagnosed on the basis of autopsy results; the subject was diagnosed as having ALS in life because of bulbar palsy and involvement of the lower and upper motor neurons in the extremities without sensory disturbance or bladder and rectal dysfunction. Several studies have reported HAM patients presenting with ALS-like features (4-9); these include a patient with bulbar palsy, systemic muscular atrophy and weakness, increased tendon reflexes of the extremities, and no sensory disturbance and a patient with bulbar palsy, systemic muscular atrophy and weakness, decreased vibratory sense in the lower legs, and impaired urination.

<table>
<thead>
<tr>
<th>Table. Cases of HAM Showing ALS-like Signs in the Literature</th>
<th>Matsuzaki et al.⁴ (n=5)</th>
<th>Vernant et al.⁷ (n=4)</th>
<th>Kuroda &amp; Sugihara⁵ (n=1)</th>
<th>Arimura et al.⁵ (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (years)</td>
<td>Mean: 52.2</td>
<td>49–77</td>
<td>57</td>
<td>67</td>
</tr>
<tr>
<td>Course (years)</td>
<td>Time to abasia: Mean: 5</td>
<td>NR</td>
<td>Time to death: 4.5 years</td>
<td>NR</td>
</tr>
<tr>
<td>Bulbar palsy</td>
<td>2/5</td>
<td>2/4</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fasciculation in tongue</td>
<td>3/5</td>
<td>NR</td>
<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>Muscular atrophy in extremities</td>
<td>5/5</td>
<td>4/4</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>5/5</td>
<td>4/4</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Babinski index</td>
<td>4/5</td>
<td>NR</td>
<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>Sensory disturbance</td>
<td>4/5</td>
<td>0/4</td>
<td>+/−</td>
<td>+</td>
</tr>
<tr>
<td>Autonomic disturbance</td>
<td>4/5</td>
<td>1/4</td>
<td>+/−</td>
<td>+</td>
</tr>
<tr>
<td>Anti-HTLV-I antibody in CSF</td>
<td>5/5</td>
<td>NR</td>
<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>Anti-HTLV-I antibody in serum</td>
<td>5/5</td>
<td>4/4</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Effect of steroid therapy</td>
<td>Improved in 2/3 treated patients</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

However, an autopsy was not performed in any of these patients. Autopsy reports on ALS-like HAM patients have described infiltration of inflammatory cells and dropout and degeneration of neural cells in the dorsal column, brain stem, cerebellum, and cerebrum in addition to the main lesions in the lateral column of the thoracic spinal cord (5, 10). Another autopsy report indicated that there were no Bunina bodies, which are unique to ALS (11).

There are two possibilities of the pathogenesis of this case: 1) HAM and ALS could have been coincidental and the inflammation process of HAM modified the ALS symptoms or 2) all of the ALS-like features were caused by HTLV-I-induced inflammation in the CNS. In the present case, the patient’s symptoms began with dyslalia at approximately 40 years of age and she became unable to speak at 52 years of age. However, she was able to communicate by writing and could still walk, suggesting a slower rate of progression than that of ALS. Matsuzaki et al. reported that the average interval between onset of disease and the inability to walk is 5 years in patients with ALS-like HAM with a high HTLV-I proviral load (Table), indicating a slower rate of progression compared to typical ALS (4). Steroid therapy was not effective in ALS-like HAM patients with a low HTLV-I proviral load similar to that in asymptomatic HTLV-I carriers, whereas in ALS-like HAM patients with a high HTLV-I proviral load, steroid therapy was highly effective with efficacy almost equivalent to that seen in typical HAM patients. The improved symptoms in our patient remained stable without deterioration by oral steroid therapy. On the basis of the high HTLV-I proviral load and the favorable response to steroid therapy, in addition to a slower progression of symptoms than that of ALS, our case was considered to be consistent with HAM presenting with ALS-like features. The measurement of neopterin and HTLV-I proviral load in HAM patients may be useful in differentiating HAM with ALS-like symptoms from ALS developing in HTLV-I carriers. Even in patients who have classical symptoms of ALS, the measurement of serum anti-HTLV-I antibody is of particular significance for differentiating HAM from ALS because half of the ALS-like HAM patients who receive steroid therapy show improvement in their symptoms.

The authors state that they have no Conflict of Interest (COI).

References