HTLV1 Associated Myelopathy, Its Diagnosis, Management and Complications

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Editorial

Human T-Cell Lymphotropic Virus Type 1 is the first discovered human retrovirus that has been isolated in 1979 from a patient with cutaneous T-Cell lymphoma. HTLV is a member of Retroviridae family in the genus Deltaretrovirus. Retroviruses are RNA viruses that produce DNA from RNA utilizing the enzyme reverse transcriptase. The DNA is subsequently incorporated into the host's genome. HTLV1 predominantly affects T lymphocytes [1,2].

Although HTLV1 is found throughout the world, its global and loco-regional prevalence is not clear. Interestingly, this loco-regional prevalence is not similar even in the areas with high endemicity rate. Clusters of high endemicity has been reported in southwestern parts of Japan, parts of the Caribbean area, foci in South America, such as Colombia and French Guyana, some areas of intertropical Africa (such as South Gabon), specific parts of the middle East (north east of Iran, i.e. Mashhad and Neyshabur), and rare isolated clusters in Melanesia. Moreover, there are clusters of highly endemic areas, located often nearby areas where the virus is nearly absent. There are evidence that its distribution follows a geographic pattern rather than the ethnicity. In general, the prevalence is about 1-6% in endemic areas, however, this sero-prevalence is gradually increased with age, approaching to 25-40% in population elder than 50 in the highly endemic areas. Besides, many seropositive cases remain asymptomatic throughout their lives without any clinical manifestation and are not discovered through regular medical visits and laboratory evaluations [3-6].

HTLV1 is transmitted at least through three recognized ways. Its sexual transmission is mostly from male to female and correlates with increased risk of sero-positivity in females with increasing age. Blood products that are contaminated with HTLV1 infected lymphocytes are another potential source of infection. The third way is its vertical transmission from mother to infant that is mainly linked to breast feeding after the age of 6 months. Contaminated blood products and breast feeding source of transmission account for 15-60% sero-positivity in transfusion recipients and 10-25% of breast fed infants of HTLV1 infected mothers, respectively [7-9].

Despite the variety in routes of exposure with variable risk of HTLV1 infection; fortunately, more than 90% of HTLV1 positive cases remain asymptomatic throughout their lives. Around 10 to 20 million HTLV1 infected cases are estimated worldwide; however, it is still unclear why a small percentage of them presented with the virus associated clinical manifestations. HTLV1 might cause 4 distinct clinical presentations; HTLV1 associated lymphoproliferative disorders (ATLL), HTLV1 associated Myelopathy/ Tropical Spastic Paraparesis (HAM/TSP), HTLV1 associated ocular disease which is mainly presented as uveitis, and cutaneous manifestations. All of these HTLV1 associated disorders present with different incidence and variable latency period among sero-positive population. ATLL, as an example, presents in around 1-4% of HTLV1 carriers. The HTLV1 associated myelopathy is even less frequent than hematologic complications with the incidence of 1-2%, respectively. The latency period for HTLV1 associated lymphoma has been reported to be as long as 20-30 years disorders. Similarly, HTLV1 associated myelopathy has a prolonged latency period of 20-30 years. However, this neurologic disorder with short latency period of 3 months has been reported in rare cases [4,10]. Co-incidence of HTLV1 associated myelopathy and lymphoproliferative disorders has not been reported.

From clinical point of view, the neurologic presentation of HTLV1 infection is a chronic inflammatory reaction of both gray and white matter in spinal cord with perivascular demyelination and axonal degeneration. It has a slowly progressive course with involvement of sensory, motor and autonomic nerves. Unlike the hematomat manifestation that shows a male predominance, the neurologic manifestation of HTLV1 is mostly reported in female patients and the average age of 40 at the time of presentation. The disease primarily presents with weakness in the lower extremities, sensory impairment with burning and tingling sensation, lumbar pain. In some cases however, urinary symptoms as well as sexual complaints might precede the weakness and sensory symptoms [11-14].

HAM/TSP is basically a chronic inflammatory disorder with a progressive nature. Indeed, the interaction between HTLV1-infected CD4+ T cells and HTLV1-specific CD8+ cytotoxic T cells (CTL), plays a critical role in the pathogenesis of HAM/TSP. Through a long-standing bystander mechanism, that eventually lead to the destruction of surrounding nervous tissues. Altered interaction between CD4+ and CD8+ T lymphocytes, as well as cytokine production seems to play a key role in its pathophysiology [15-17].

Clinical studies have shown that CD4+ T cells in the peripheral blood of HAM/TSP patients, particularly HTLV1-infected CD4+ T cells, have an exaggerated transmigrating activity with the ability to accumulate in the tissues such as central nervous system. It has also been observed in several studies that the pro-viral load in the peripheral blood samples of HAM/TSP patients is significantly higher than asymptomatic HTLV1 infected cases. Moreover, examination of the cerebrospinal fluid (CSF) of HAM/TSP patients has been reported higher percentage of HTLV1-infected cells in CSF compared with peripheral blood mononuclear cells (PBMC) with a pro-viral load ratio of more than 10% in CSF vs. more than 1% in peripheral blood mononuclear cells, respectively. This ratio has been reported to be less than 10% (CSF) and less than 1% (PBMC) in asymptomatic HTLV1 carriers in comparative studies [18-20].

Diagnosis of HAM/TSP is based on the clinical signs and symptoms of upper motor neuron lesions, such as spasticity, Babinski sign and...
stones are significantly high among these patients. Low back pain is a prominent symptom in HAM/TSP patients that has been reported in up to 75% of patients. It is exacerbated with movements and interferes with patients' physical activity and has a significant negative impact in their quality of life. Analgesics, antidepressants, gabapentin and even corticosteroids have been proposed as a potential treatment for this pain with different efficacy [29-31].

HAM1V1 is a retrovirus capable of causing a wide range of clinical manifestations, with at least two distinct categories of lymphoproliferative disorder and inflammatory myelopathy. The pathophysiology of these two clinical presentations, as well as the therapeutic approach and prognosis are quite different. Fortunately, among over 20 million sero-positive cases of HTLV1 worldwide, less than 5% of this infected population is at risk of these clinical diseases. Why these cases are prone to the clinical disease while a vast majority remains asymptomatic healthy infected throughout their lives is a puzzle, however, early acquisition of the virus during the childhood and high pro-viral load are among the possible etiologies. HAM/TSP is a chronic inflammatory myelopathy with sensory, motor and autonomic components that more commonly affect women. Different therapeutic approaches have been suggested and tried in these patients with different responsiveness. However, the disease causes morbidity in many people in endemic areas of the world. Apart from therapeutic approach, supportive care and rehabilitation is an important clinical need in this group of patients. Novel approaches such as cannabinoids with their anti-spastic, analgesic, and immune modulatory effects might be beneficial for symptomatic management of these patients. Further clinical studies are mandated to address these unmet clinical needs.

References


