HTLV-1 and Neurological Conditions

When to suspect and when to order a diagnostic test for HTLV-1 infection?

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Abstract – HTLV-1 is a retrovirus associated with a myriad of clinical conditions, especially hematological and neurological ones. Regarding nervous system diseases, it is of utmost importance to select those cases in which HTLV-1 infection could really be associated. This is particularly true for patients from endemic areas and for HIV-infected patients and drug users, since these groups are at a higher risk for HTLV infection. This caution in selecting neurological patients for HTLV diagnostic tests is justified by the fact that in some circumstances the seropositivity may merely represent an epiphenomenon. In this paper we enroll some neurological conditions that have been associated with HTLV-1/2 infection in the literature and discuss the real need for HTLV-1/2 diagnostic tests in each one. Because HIV/HTLV-co-infected patients seem to be at an increased risk for neurological diseases development, a special consideration about this matter is also made.

KEY WORDS: HTLV, myelopathy, myopathy, peripheral neuropathy, HIV.

Doenças neurológicas e infecção pelo HTLV-1: quando suspeitar e quando solicitar testes diagnósticos para a infecção pelo HTLV-1

Resumo – O HTLV-1 é um retrovírus associado tanto a doenças hematológicas quanto a doenças neurológicas. Em relação às doenças neurológicas, é fundamental que selecionemos aquelas em que de fato a infecção pelo HTLV-1 possa ser a causa. Isto é particularmente verdadeiro nos pacientes oriundos de áreas endêmicas e nos pacientes infectados pelo HIV e usuários de drogas, haja vista que estes grupos são de risco para infecção pelo HTLV. Este cuidado ao selecionarmos aquelas condições neurológicas que merecem ser investigadas com sorologia para o HTLV se justifica pelo fato de que nem sempre podemos afastar uma associação fortuita entre a infecção e a referida doença. Neste artigo, comentaremos sobre algumas condições neurológicas que podem estar associadas com a infecção pelo HTLV-1/2, discutindo a real necessidade de solicitar testes para o diagnóstico da infecção pelo HTLV-1/2 frente a elas. Uma breve consideração sobre a co-infecção HIV/HTLV será feita no final deste artigo tendo em vista que estes pacientes apresentam um risco aumentado para o desenvolvimento de doenças neurológicas.

PALAVRAS-CHAVE: HTLV, mielopatia, miopatia, neuropatia periférica, HIV.

The human T cell lymphotropic virus type 1 (HTLV-1) is a retrovirus and the etiologic agent of both a group of hematological disorders known as Adult T cell leukemia/lymphoma (ATLL) and a group of neurological conditions known altogether as the HTLV-1 neurological complex, of which the most common is the HTLV-1 associated myelopathy/Tropical spastic paraparesis (HAM/TSP). Endemic infection with HTLV-1 is now recognized to be worldwide, and is also common in Brazil. The number of people around the world infected with HTLV-1 is estimated as being between 10 to 20 million. There are areas in Japan, sub-Saharan Africa, the Caribbean, and South America where more than 1% of the general population is infected. The overall HTLV-1 seroprevalence among blood donors in Brazil is approximately 0.45%. However, these rates vary, from 0 to 1.8%, depending on the region.

Although the majority of HTLV-1 carriers remain asymptomatic for the rest of their lives, the cumulative lifetime risk of developing ATLL or HAM/TSP is around 5%. HTLV-1 can be transmitted from mother to child, during sexual intercourse, and through contaminated blood products. HTLV-1 has a special tropism for CD4+ lymphocytes and uses GLUT-1, the ubiquitous vertebrate glucose transporter, as the main receptor to infect cells. It is trans-
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transmitted from cell to cell through a viral synapse and enters target cells via interaction with GLUT-1 in association with Neuropilin-1 (NRPI), the receptor for semaphorin-3A, and VEGF-A165, a member of the immune synapse. GLUT1, NRPI, and the HTLV-1 envelope protein form ternary complexes in transfected cells.

The diagnosis of HTLV-1 infection can be made either by serological tests (ELISA and Western Blot [WB], Immunofluorescence, Particle Agglutination), by detection of the HTLV-1 genome (Polymerase Chain Reaction - PCR) or by virus isolation. The sensitivity for diagnosis of HTLV-1 is higher with ELISA than with WB. Some serologic tests yield high rates of false-positive results. Therefore, a few authors believe that PCR can be more sensitive than serology for this diagnosis. PCR should therefore be considered for selected HTLV-I antibody-negative patients with unexplained spastic myelopathy or T-cell neoplasia. Although a positive ELISA requires a further confirmation by WB, this test still gives a high percentage of indeterminate results. In the cerebrospinal fluid (CSF) diagnosis can be made either by ELISA/WB alone or by a combination of PCR in the CSF and the intrathecal synthesis of antibodies to HTLV-1 by the antibody index (AI). Cases of HAM/TSP may have increased AI for HTLV-1 and the presence of HTLV-1 proviral sequences in CSF by PCR.

The present review aims to provide neurologists with data that can assist them to choose those clinical neurological circumstances that could be most probably due to HTLV-1 infection. In these instances, HTLV-1 testing should be ordered to clarify the diagnosis.

**ACUTE DISSEMINATED ENCEPHALOMYELITIS**

Generally speaking, acute disseminated encephalomyelitis (ADEM) is a monophasic demyelinating disease of the central nervous system that commonly follows immunization or infections. Several pathogens have been implicated in this condition such as enteroviruses, herpes simplex viruses, hepatitis A virus, Epstein Barr virus, influenza, measles, mycoplasma, rubella, and varicella zoster. There are only a few reports of ADEM in HTLV-1 infected patients and it is not clear if the virus is directly implicated in the demyelinating process or if HTLV infection is only a epiphenomenon. So, to date there is no hard evidence for proposing routine HTLV-1 tests in ADEM patients.

**ENCEPHALOPATHY AND COGNITIVE DEFICITS**

The first reports of brain MRI lesions in HAM/TSP patients appeared shortly after the initial HAM/TSP descriptions. The prevalence of these lesions is said to be around 50% to 80%, suggesting that the inflammatory response against HTLV-1 may not be restricted to the spinal cord.

The interest for cognitive disturbances in HTLV-1 infection started after a number of reports describing these brain MRI abnormalities in patients with HAM/TSP. Because the white matter lesions of HAM/TSP are somehow similar to those observed in patients with multiple sclerosis or in HIV infected people (both conditions with well known cognitive impairment), cognitive deficits in HAM/TSP patients were also suspected. Most of the published papers about cognitive disturbances in HAM/TSP describe psychomotor slowing, attention deficits as well as visual and working memory deficits. In the only controlled study using an extensive neuropsychological battery, HTLV-1 infection was associated with mild cognitive deficits characterized by impairments in psychomotor speed, verbal fluency, verbal and visual memory, selective and alternate attention (flexibility), and visuconstructive abilities.

We suggest that in endemic areas HTLV-1 testing should be performed in patients with myelopathic symptoms and signs, brain white matter abnormalities on MRI, and mild, subcortical cognitive deficits.

**MENINGEAL SYNDROMES**

Subacute meningitis can be rarely seen in patients with HTLV-I infection. Most patients presented a decreased level of consciousness and a stiff neck. The proposed mechanism is meningeal lymphomatous infiltration, similar to that found in ATLL. Hence, HTLV-I testing should be considered in patients with subacute meningitis with mononuclear predominance in areas with a high prevalence of HTLV-I infection, particularly in those individuals with leukemia or lymphoma.

**ACUTE SPASTIC PARAPARESIS**

HAM/TSP is classically described as a chronic myelopathy with insidious onset and a slow evolution over years. Nevertheless, patients with acute or subacute evolution over days to weeks have been described. The prevalence of subacute evolution was estimated in 7.9% in a reference center for HTLV in Rio de Janeiro, Brazil. The factors related to such aggressive course are not completely understood, but recently we have demonstrated that patients with acute or subacute evolution have HTLV-1 proviral load quantification similar to patients with typical evolution. We believe that patients with acute, non-compressive myelitis should be tested for HTLV-1, especially if tests for other causes are inconclusive.

**PROGRESSIVE SPASTIC PARAPARESIS**

HTLV-1 is the main cause of chronic progressive spastic paraparesis in Brazil. The first Brazilian nationwide study on the disease concluded that (1) HAM/TSP was more prevalent among women and whites, (2) the most important risk factors for infection were sexual promiscuity and blood transfusion, and (3) although a remarkably uniform
disease throughout the country is observed, some statistically significant differences were detected such as a higher proportion of females over males in the Northeast region, a higher proportion of whites in the Southeast and in the South while in the Northeast infection predominates in the mulattos, and a high rate of venereal diseases in the Southeast region and of intravenous drug use in the South.

The typical patient in whom a search for HTLV-1 infection should be sought is the one with a slowly progressive and non-compressive paraparesis in the lower limbs, widespread pyramidal signs (i.e., in upper and lower limbs), urinary urgency or incontinence, constipation, and subtle objective sensory signs (mainly decreased vibration sense). A clear-cut sensory level may occur but is exceedingly rare. Some patients complain of lumbar pain, sometimes with radicular radiation down to the legs. This pain, which occasionally can be very disabling, has a combination of neuropathic and mechanical features. For a more detailed account of clinical features and diagnostic guidelines for HAM/TSP the reader is referred to other sources.

CONUS MEDULLARIS SYNDROME

Conus medullaris lesions lead to early sphincter disturbances (flaccid bladder, constipation), impotence, and saddle anesthesia with mild motor disturbances. Common causes include disc herniation, tumors, and fractures at L2 level. In HAM/TSP patients, thoracic spinal cord is the most affected site by the inflammatory process and a complete conus medullaris syndrome is not usually seen in these patients. However, patients may present with bowel or bladder symptoms as first manifestations of HAM/TSP in the absence of motor complaints, which can sometimes suggest involvement of the conus. Thus, we recommend HTLV-1 testing in patients with conus medullaris syndrome and no apparent lesion on the lumbar spine MRI.

AMYOTROPHIC LATERAL SCLEROSIS (ALS) SYNDROME

ALS syndrome in HTLV-1 infection has been described since 1991, but in some cases an epiphrenon cannot be excluded. Typically, HTLV-1-infected patients with symptoms and signs suggestive of ALS have a high HTLV proviral load and present symptoms and signs suggestive of HAM/TSP jointly with symptoms and signs typical of ALS, i.e. muscle atrophy, fasciculation, and cramps. In general, these patients tend to evolve more slowly than typical, non-infected ALS patients. Thus, we suggest that patients from endemic areas with symptoms and signs suggestive of both upper and lower motor neuron disorder jointly with sensory symptoms and/or bladder dysfunction should be routinely tested for HTLV antibodies.

MYOPATHIES

Although the most frequent site of nervous system lesion in the HTLV-1 infection is the thoracic spinal cord, which leads to the development of HAM/TSP, the virus may affect all components of the neuroaxis, including muscles. Muscle damage is not related to direct invasion of muscle fibers by the virus, but to an immune-mediated process. Classically, both polymyositis (PM) and inclusion body myositis (IBM) have been associated with HTLV-1 infection. Furthermore, clinicians may also consider ordering HTLV-1 testing in the context of isolated cramps without other features of myopathy and in patients with persistent serum creatine phosphokinase (CK) elevation.

The clinical presentation of HTLV-1-related PM is similar to that of idiopathic PM. Symmetrical and proximal weakness and varying degrees of myalgia are usually seen early in the disease. Bulbar muscles are clinically affected in one third of the cases. Deep tendon reflexes are diminished or abolished but may be normal or even brisk in patients with concomitant HAM/TSP. Other manifestations such as rheumatologic (arthritis, Raynaud’s phenomenon), cardiac (myocarditis), and respiratory (pneumonitis) complications are present in HTLV-1-related PM, but they are less frequent than in HTLV-1-seronegative PM.

IBM occurs predominantly in males over 50 years of age. Onset is insidious and slowly progressive, which can delay diagnosis. Proximal and distal muscles are affected asymmetrically. Quadriceps, volar, and ankle dorsiflexors muscles are affected early. Extraocular muscles tend to be spared. One third of patients have a mild sensory neuropathy. CK levels are minimally elevated or normal in most affected individuals.

Persistent cramps may be found in several metabolic, genetic, and inflammatory myopathies. Occasionally, isolated muscle cramps are the first sign of HAM/TSP and may be present years before the development of overt myelopathy. Though there is no hard evidence, clinicians may consider ordering HTLV-1 testing in patients with muscle cramps from endemic areas after exclusion of other etiologies.

Persistently increased serum CK levels usually reflect the presence of neuromuscular disease. Chronic elevation of serum CK is occasionally encountered in apparently healthy individuals with no evidence of muscle disease on clinical and laboratory evaluation. In large series of patients with CK elevation, HTLV-1 infection was not observed in none of the patients, but these studies came from areas with a low prevalence of HTLV-1 infection. Glynn et al. have demonstrated higher serum CK levels in HTLV-1/2 infected blood donors when compared with non-infected individuals. CK elevation in HTLV-1 carriers is usually associated with clinical evidence of myopathy, but in a setting of endemic infection is reasonable to
consider HTLV-1 testing in individuals with persistent serum CK elevation.

In summary, while there is large evidence for advice HTLV-1 testing in patients with PM and IBM, one may consider investigation in individuals with persistent cramps or serum CK elevation in areas with high prevalence of HTLV-1 infection.

PERIPHERAL NERVOUS SYSTEM DISEASES

The reported prevalence of peripheral neuropathy (PN) in HTLV-1 infection has varied from negligible to 32%44,45. Majority of cases are presently seen in association with HAM/TSP, but isolated PN has been reported46. Furthermore, a higher prevalence of PN in HIV/HTLV-2 co-infection was described, suggesting that HTLV-2 could be a predisposing cofactor for development of PN in HIV-infected patients. Since HTLV-1 and HTLV-2 share genetic homology the same could be expected in HIV/HTLV-1 co-infection17.

At present there is no evidence of direct viral infection of the peripheral nervous system. In addition, previous studies demonstrated that spinal nerve roots are also involved in the inflammatory process that causes HAM/TSP46. Therefore, either a proximal or a distal inflammatory mechanism may be responsible for PN associated with HAM/TSP. Lymphocytic infiltrates have been observed in both spinal cord and muscle tissues in patients with HTLV-1-associated polymyositis. Axonal atrophy demyelination, remyelination, and perineural fibrosis in sural nerve biopsy specimens from HAM/TSP patients with PN has been reported46. More recently, Kiwai et al. described 9 biopsy-proven cases of PN in association with TSP/HAM46. Sural nerve pathology of these individuals revealed a combination of demyelination and remyelination, and axonal degeneration and regeneration. They also failed to demonstrate inflammatory infiltrates in these samples.

PN associated with HTLV-1 is characterized by paresthesiae, burning sensations, and abnormal superficial sensation distally in a stock-and-glove distribution, coupled with abolished ankle jerks. Cases of acute or chronic polyradiculo-neuropathy and chronic sensory neuropathy presenting as severe impairment of proprioceptive and kinesthetic sensation associated with HTLV-1 have been described, but there is uncertainty about the role of the infection in the pathogenesis of these neurological conditions.

In summary, according to the aforementioned evidences we strongly suggest that patients from endemic areas with PN symptoms or signs should be routinely investigated for HTLV-1 infection.

CRANIAL NEUROPATHIES

Even in HTLV endemic areas there are no sufficient data to advice a routinely HTLV antibodies tests in isolated cranial neuropathies. Although a few reports have showed peripheral facial palsy in HTLV infected patients, an epiphemomenon could not be excluded49,53. The only exception seems to be a simultaneous involvement of optic nerve and spinal cord such as the one observed in Devic’s disease52. In this situation we recommend HTLV-1/2 antibodies testing (ELISA/WB) both in serum and in CSF.

MOVEMENT DISORDERS

Although some extrapiramidal syndromes such as Parkinsonism, essential tremor, and myoclonus have been described in a few infected patients, a causal relationship between HTLV infection and these movement disorders is presently obscure53,54. So, even in endemic areas HTLV antibodies tests would not be necessarily done in patients with movement disorders and lack of evidence of other neurological abnormality definitely associated with HTLV-1/2.

AUTONOMIC DYSFUNCTION

There are strong evidences supporting autonomic dysfunction in HTLV-1/2 infection. Reports have showed orthostatic hypotension, lack of sweat control, and neurogenic bladder dysfunction, the majority of them in association with HAM/TSP52-59. Neurogenic bladder dysfunction has also been showed in HTLV-1-infected patients without HAM/TSP34. So, in endemic areas we advice HTLV-1 antibodies tests in patients exhibiting autonomic dysfunction of unknown cause.

MULTIPLE SCLEROSIS PATIENTS

To rule out HTLV-1 infection is mandatory in any patient with symptoms and signs suggestive of multiple sclerosis (MS). The question here is if the clinical picture is due to MS or due to HAM/TSP in an HTLV-1-infected patient. This differentiation is quite difficult especially if we consider the myelopathic, primary progressive form of MS50. Maybe in these patients HTLV-1 proviral load measurements could be useful, since HAM/TSP patients exhibit higher level of proviral loads than MS patients sero-positive to HTLV-151.

HIV INFECTION

In addition to the fact that HTLV and HIV share a common tropism for T cells and exhibit similarity on modes of transmission, both have the potential to affect the nervous system. However, HTLV-1 is cell proliferative, poorly replicative, and genetically stable, whereas HIV-1 has the opposite behaviour52.

Since the beginning of the HIV epidemic, neurological disorders have been reported as very frequent and disabling among AIDS patients50. For example, the nervous system is affected in 26% to 94% of HIV-infected individuals in Brazil54. As a result, since both HTLV and HIV are
associated with neurological disorders, there is a reason-
able concern about an increased risk of neurological dis-
eases among HIV/HTLV-coinfected individuals.

Regarding neurologic diseases in coinfected individu-
als, there are some papers pointing to a higher prevalence
of myelopathy in coinfected individuals when compared
to monoinfected HIV patients. In 9 coinfected individu-
als authors described 2 HIV/HTLV-1 and one HIV/HTLV-2-
coinfected patients with a slowly progressive myelopathy
resembling HAM/TSP. In other transversal study, 73% of
15 coinfected subjects had evidences of myelopathy ver-
sus 16% of 62 HIV monoinfected individuals (OR=13.0). Per-
ipheral neuropathy was also more prevalent among
coinfected than monoinfected individuals. More recent-
ly, in a large cohort (62 HIV/HTLV-1 and 141 HIV/HTLV-2
coinfected patients) followed for many years, Beilke et
al. verified that coinfected patients were more likely to
present neurologic complications than HIV-infected in-
dividuals, mainly peripheral neuropathy. Similar results
were reported by Zehender et al. who studied 30 HTLV-2/
HIV-coinfected patients for 28 months. They reported an
increased risk of developing peripheral neuropathy (OR
3.3), and during the period of observation one coinfected
patient developed myelopathy.

So, since that both HIV and HTLV share similar infec-
tion routes and are prone to cause neurological diseases,
HTLV antibodies should be investigated in every HIV in-
fected patient and vice-versa.

### CONCLUSIONS

Table summarizes the main conditions in which HTLV
testing should be sought. HTLV-1/2 infection is associated
with a variety of neurological disorders and can confuse a
precise clinical judgment in some circumstances, partic-
ularly in MS patients and in patients with non-compres-
sive chronic spastic paraparesis. Also, co-infection with
HIV can increase the risk for neurological disease, name-
ly myelopathy and peripheral neuropathy. Therefore, it is
important for the neurologist to be aware of those neu-
rological conditions in which HTLV-1/2 antibodies tests
should be included in the neurological investigation, par-
ticularly in endemic regions.

### Table. When to investigate HTLV-1 infection in neurological conditions.

<table>
<thead>
<tr>
<th>Neurological picture</th>
<th>Testing for HTLV-I</th>
<th>Observation</th>
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<tbody>
<tr>
<td>ADEM</td>
<td>+</td>
<td>In patients with subcortical cognitive deficits, particularly in those with myelopathic symptoms</td>
</tr>
<tr>
<td>Cognitive deficits</td>
<td>+</td>
<td>In patients from endemic areas for HTLV and with leukemia or lymphoma</td>
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<tr>
<td>Meningeal syndromes</td>
<td>+</td>
<td>Specially in patients with non-compressive myelopathies</td>
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<tr>
<td>Acute spastic paraparesis</td>
<td>++</td>
<td>In individuals with a normal lumbar spine MRI</td>
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<tr>
<td>Progressive spastic paraparesis</td>
<td>+++</td>
<td>Specially in atypical cases, i.e., patients with bladder dysfunction, for example</td>
</tr>
<tr>
<td>Conus medullaris syndrome</td>
<td>++</td>
<td>Particularly in endemic regions for HTLV-1 infection</td>
</tr>
<tr>
<td>ALS</td>
<td>++</td>
<td>Specially in those with chronic, idiopathic, mainly sensory and axonal PN</td>
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<tr>
<td>Polymiositis</td>
<td>+++</td>
<td>Particularly in those with the chronic primary progressive, myelopathic form</td>
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<tr>
<td>IBM</td>
<td>++</td>
<td>In asymptomatic individuals or in patients with persistent cramps</td>
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<tr>
<td>Isolated PN</td>
<td>++</td>
<td>Persistently elevated CK in asymptomatic individuals or in patients with persistent cramps</td>
</tr>
<tr>
<td>Isolated cranial neuropathies</td>
<td>0</td>
<td>Particularly in endemic regions for HTLV-1 infection</td>
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<tr>
<td>Movement disorders</td>
<td>0</td>
<td>Persistently elevated CK in asymptomatic individuals or in patients with persistent cramps</td>
</tr>
<tr>
<td>Idiopathic autonomic dysfunction</td>
<td>++</td>
<td>Persistently elevated CK in asymptomatic individuals or in patients with persistent cramps</td>
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<tr>
<td>MS</td>
<td>+++</td>
<td>In those with subcortical cognitive deficits, particularly in those with myelopathic symptoms</td>
</tr>
<tr>
<td>HIV infection</td>
<td>+++</td>
<td>In those with subcortical cognitive deficits, particularly in those with myelopathic symptoms</td>
</tr>
</tbody>
</table>

0, not necessary; +, only in special situations (see text); ++, advisable; +++, mandatory; ADEM, acute disseminated encephalomyelitis; ALS, amyotrophic lateral sclerosis; IBM, inclusion body myositis; CK, creatinekinase; PN, poly neuropathy; MS, multiple sclerosis; HIV, human immunodeficiency virus.


