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TUBERCULOUS MENINGOENCEPHALOMYELITIS AND COINFECTION WITH HTLV-I + HTLV-II

Case report

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ABSTRACT - HTLV-I and HTLV-II are endemic in some areas of Brazil, where an associated disease, HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) have been diagnosed in significant number of infected individuals. Tuberculosis has been demonstrated among those individuals, with higher prevalence than in the general population, suggesting that there is an increased risk for this comorbidity. We report the case of an individual coinfected with HTLV-I and HTLV-II, suffering from an insidious meningoencephalomyelitis caused by *Mycobacterium tuberculosis.* The patient was a 44 years old man successfully treated with steroids and antituberculous drugs, improving clinically and turning to a negative PCR and to a normal blood-cerebrospinal fluid barrier.

KEY WORDS: neurotuberculosis, myelopathy, cerebrospinal fluid, HTLV-I, HTLV-II.

Meningoencefalomielite tuberculosa e coinfecção por HTLV-I + HTLV-II: relato de caso

RESUMO - Os vírus HTLV-I e HTLV-II são endêmicos em algumas regiões do Brasil, onde uma das doenças associadas, a paraparesia espástica tropical/mielopatia associada ao HTLV (PET/MAH), tem sido diagnosticada em significativo número de pacientes infectados. Nesses indivíduos, a prevalência de tuberculose é maior que na população geral, sugerindo que possa haver um maior risco para esta comorbidade. Relatamos o caso de um homem de 44 anos coinfectado HTLV-I + HTLV-II que desenvolveu meningoencefalomielite por *Mycobacterium tuberculosis.* O paciente apresentou recuperação clínica parcial, correção da disfunção de barreira hemato-liquórica e negativação no PCR, mediante o tratamento com corticoesteróides e tuberculostáticos.

PALAVRAS-CHAVE: neurotuberculose, mielopatia, liquido cefalorraqueano, HTLV-I, HTLV-II.

Human T-cell lymphotropic virus type I and II (HTLV-I and HTLV-II) are retrovirus belonging to the genus *Deltaretrovirus.* HTLV-I is linked to a lymphoproliferative disease, adult T-cell leukemia/lymphoma (ATLL). HTLV-I and HTLV-II are responsible for immunomediated diseases, the prototype being HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP)[1]. HTLV-II has been associated to sporadic cases of progressive myelopathy, although with low grades of disabilities and sensory ataxia[2]. HTLV-I is a more cosmopolitan virus, with endemic areas in the south of Japan, central areas of Africa, some Caribbean islands, and South America. HTLV-II is endemic in native populations of Africa (Pygmy) and America (Amerindians), besides intravenous drug users (IDUs) from United States (USA), Europe and Southeast Asia[2,3]. In Brazil, where the mandatory screening of HTLV-I/II was introduced in 1993, the prevalence among blood donors demonstrated a wide regional variation, from 0.08% to 1.35%. The city of Porto Alegre, capital of the southernmost state of the country, Rio Grande do Sul, has a prevalence of 1.27% of infection for HTLV-I/II; HTLV-I representing 83%, and HTLV-II, 17% of the individuals infected with *Deltaretroviruses*[3].

Some studies have suggested that the infection with HTLV-I can be associated with immunosuppression, increasing the risk and expression of other infectious diseases. A decrease in delayed-type hypersensitivity to *Mycobacterium tuberculosis* has been demonstrated among some HTLV-I-infected individu-

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als, as well as a high prevalence of HTLV-I/II infection among tuberculosis patients[4]. However, some studies have failed to establish an association between tuberculosis and HTLV-I or HTLV-II infection[5].

The aim of this report is to present a striking occurrence of tuberculous meningoencephalomyelitis in an immunocompetent patient with previous subclinical myelopathy and uveitis due to HTLV-I and HTLV-II double infection.

CASE

In August 1995, a 44 year-old Caucasian man was presented to our HTLV outpatient clinic for counseling, due to a positive ELISA test for HTLV-I/II infection (ELISA Murex HTLV-I+II, Murex Diagnostics, Dartford, UK), at the last blood donation. He tested negative for HIV-1. Confirmatory tests were then performed: western blot (WB) in serum (HTLV Blot 2.4, Genelabs Diagnostic, Singapore) and polymerase chain reaction (PCR in house) from peripheral blood mononuclear cells (PBMC) were positive for HTLV-I and HTLV-II double infection. His mother and his wife tested negative for HTLV-I/II. He described a past history of intravenous drug use (IDU), recurrent unilateral uveitis (2 relapses treated with prednisone) since 1990 and mild micturitional symptoms (pollakiuria and nocturia) since 1994. The neurological examination reveled brisk reflexes in the lower limbs, flexor plantar reflexes, abolished superficial abdominal reflexes and normal sensory examination.

In November 1996 he complained of gait instability and there were increased brisk reflexes and sensory ataxia. We performed the first lumbar puncture and the cerebrospinal fluid (CSF) analysis showed an inflammatory pattern: 6 cells/mm^3, total protein content=31 mg/dL, Q_{ALB} (albumin quotient)= 4.2x10^{-3}, IgG Index=1.1, IgG_{IF} (intrathecal fraction of IgG)= 39%[6]. ELISA and WB were positive, including p19, p24, gd21, MTA-1 and K55 bands. Somatosensory evoked potentials of the lower limbs were normal. He neglected continuing the investigation.

In March 1998 he was admitted to another hospital due to a subacute development of left hemiparesis, mental confusion, dizziness, incoordination, headache, urinary retention, obstipation and hypoacusis. A brain computed tomography (CT) scan showed a small infarction in the territory of the right medial striate artery; a myelography and a spinal CT scan were normal. The CSF examination showed 1,000 cells/mm^3 (60% lymphocytes), total protein content=577 mg/dL. His provisional diagnosis was "meningoencephalitis associated to HTLV infection" and he was discharged from that institution only with supportive medication. Two months later he returned to us presenting an ataxic gait, right paresthesia, hypopalesthesia and hypoesthesia at the lower limbs with a T10 level, nocturnal spasms, and erectile dysfunction. Once more he tested negative for HIV-1, the chest X-ray was normal and the purified protein derivative skin reaction (PPD test) showed a strong reaction. There was a left anacusia and a severe right disacusia at the auditive exam. We obtained a positive PCR result for *M. tuberculosis* in the CSF and identified a significant blood-CSF barrier dysfunction, characterized by an increase in total protein content and in albumin quotient, strongly suggestive of bacterial meningitis. The patient started receiving antituberculous chemotherapy (rifampin + isoniazid + pyrazinamide for 10 months), prednisone 60 mg/day (for five months) and physical therapy. He denied prior history of tuberculosis.

One month later, because of a progressive improvement in gait and micturition function, we got the fourth CSF sample (June 1998): the PCR test remained positive for M. tuberculosis, 80 cells/mm^3 and total protein content=73 mg/dL.

In January 1999, a new CSF analysis (5th) disclosed 16 cells/mm^3, total protein content=57 mg/dL, a normal blood-CSF barrier (Q_{ALB}) and an IgG intrathecal synthesis (IgG-Index =1.6 and IgG_{IF}=55%). Because of the persistence of nocturnal flexor spasms in the lower limbs we introduced baclofen 30 mg/day and pentoxyphilline 800 mg/day, and in August, it was possible to note an improvement in position and vibratory sense. The chest X-ray remained normal. In November 1999, the sixth CSF examination showed an IgG-Index= 0.6 and IgG_{IF}=0%. He persisted with a left hemiparesis, hypoacusis, sexual dysfunction and nocturia.

DISCUSSION

HTLV-I is the main etiologic agent of non-traumatic and non-tumoral progressive myelopathies in Brazil, partially due to its high prevalence in endemic areas[3]. HTLV-II has also been associated, although with lower frequency than HTLV-I, to inflammatory diseases of spinal cord[2,3].

Tuberculosis, caused by *Mycobacterium tuberculosis,* is an ancient disease but remains one of the major world health problems; its resurgence during the past decade is largely due to the HIV-1 infection. About 15% of patients with tuberculosis have extrapulmonary disease, and 6% of these have neurological involvement. Tuberculous meningoencephalomyelitis is the least common form of neurotuberculosis, even among AIDS patients[7]. In the review of Marsh[8], he suggested that those individuals infected with HTLV-I might be at increased risk of tuberculosis, in part because of the suppression of tuberculin skin reaction in asymptomatic carriers infected with HTLV-I. HTLV-II infection has been linked to soft tissue abscess, pneumonia, and tuberculosis among IDUs[9].

In this case report we have presented an individual coinfected with HTLV-I and HTLV-II who developed a subclinical HTLV-associated myelopathy. Meanwhile he acquired an acute meningoencephalomyelitis, preliminarily attributed to HTLV-I/II infection, even with the cerebrospinal fluid markedly abnormal, differing from the common CSF profile in HTLV-infection (mild or no pleocytosis, normal or mild increase in protein content and IgG-intrathecal synte-

Table. Serial cerebrospinal fluid analysis.

	Unit	Nov 1996	Apr 1998	May 1998	Jun 1998	Jan 1999	Nov 1999
Exam number		1	2	3	4	5	6
Cells	/mm^3	6	1,000	173	80	16	17
Protein	mg/dL	31	577	147	73	57	46
Q_{ALB}	x 10^{-3}	4.2	ND	18.5	ND	5.0	6.5
IgG index		1.1	ND	0.5	ND	1.6	0.6
IgG_{IF}	%	39	ND	0	ND	55	0
PCR $_{M. tuberculosis}$		ND	ND	+	+	–	–

ND, not done; +, positive result; –, negative result; Q_{ALB}, albumin quotient; IgG_{IF}, intrathecal fraction of IgG; PCR, polymerase chain reaction.

sis)[10,11]. Fortunately he survived, in spite of receiving just supportive treatment, initially. Some sequels like deafness, hemiparesis and micturitional disorders have persisted. In the sequence of the investigation, we detected, by PCR, the presence of *M. tuberculosis,* configuring it as the causal agent. We believe that the severe evolution of the subclinical myelopathy associated with HTLV-I and HTLV-II double infection was related to an inflammatory disease due to the superimposed tuberculosis of the central nervous system (CNS). Therapeutic response to the combination of antituberculous drugs and prednisone determined the complete resolution of that infection, as shown by a negative PCR and by means of the evident clinical improvement and characteristic modifications in the cerebrospinal fluid exam.

Serial CSF analysis (Table) showed, initially, the typical mild inflammatory pattern associated to HTLV-I or HTLV-II infection (IgG intrathecal synthesis with 39% of intrathecal fraction). Afterwards, developing neurotuberculosis, it had evolved to marked pleocytosis, decrease in glucosis quotient and severe blood-CSF barrier dysfunction. By beginning appropriate drugs, there was a progressive normalization of the barrier and the maintenance of IgG intrathecal synthesis (55% of intrathecal fraction) until the sixth CSF exam, when it returned to the normal pattern. The improvement in the CSF profile associated to the negative results of the PCR exams convinced us about the complete resolution of CNS infection with *M. tuberculosis.*

A high index of suspicion is essential for the diagnosis of neurotuberculosis because the clinical manifestations are protean and nonspecific. Nevertheless, the clinical findings of cranial nerves involvement, cerebellar signs and inflammatory CNS lesions on brain CT or MRI may suggest the possibility of associated tuberculous infection.

In the work-up of suspected tuberculous meningoencephalomyelitis, a complete CSF examination is mandatory, along with PCR for *M. tuberculosis* and neuroimaging, as described here and reported by others[7]. On the other hand, additional investigation of other pathogens and diseases are imposed, even in the presence of HTLV-I/II infection in endemic areas, when the cerebrospinal fluid analysis substantially differed from the common HTLV-I/II profile[10,11].

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