SHORT REPORT

HTLV-I infection and neurological disease in Rio de Janeiro

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Abstract

Fifty patients with chronic neurological diseases attending a clinic in Rio de Janeiro, Brazil, were examined for evidence of HTLV-I infection. Fifteen of 27 with progressive paraparesis of obscure origin had antibodies to HTLV-I in high titre in their serum samples, and 10 of 13 studied had antibodies in their cerebrospinal fluid. The clinical features of the antibody positive patients were similar to those of patients with HTLV-I associated myelopathy from other countries except that half of the Brazilian patients were white. Seven patients had multiple sclerosis and one of these had antibodies to HTLV-I in the serum. None of the eight patients with motor neuron disease and four with polymyositis had HTLV-I antibodies in their serum samples.

Patients and methods

Fifty patients with a diagnosis of paraparesis of obscure origin, multiple sclerosis, amyotrophic lateral sclerosis (motor neuron disease), and polymyositis who were attending an outpatient clinic were studied. The neurological diagnosis was made without knowledge of the HTLV-I status. Of the 50 patients, 46 had adequate serological specimens taken. All had extensive clinical, laboratory, and radiological investigations, and all those with paraparesis of obscure origin had at least one normal full length myelogram. HTLV-I antibodies were sought by enzyme linked immunosorbent assay (ELISA) and western blot analysis. The ELISA was performed with the Dupont commercial HTLV-I ELISA kit, which is a modification of the Saxinger and Gallo assay.¹⁵ End point titres were defined as the greatest dilution of serum to give a positive ELISA reading. Western blotting was performed as previously described¹⁶ with a lysate from an HTLV-I infected line (HUT 102).

Results

The clinical diagnoses were paraparesis of unknown cause (27 patients), multiple sclerosis (seven), motor neuron disease (eight), and polymyositis (four). Fifteen of 27 patients with paraparesis of unknown cause had high titres (10^{-4} to 10^{-6}) of HTLV-I antibodies in their serum, and 10 of 13 tested had antibodies in the cerebrospinal fluid (CSF titres $10^{-1.4}$ to 10^{-4}). None of the patients with other neurological conditions had HTLV-I antibodies in the serum or CSF with the exception of one patient with a diagnosis of MS who had a progressive paraparesis with a history of blurred vision but in whom there was no clinical abnormality of the cranial nerves at the time of this study. Demographic data relating to these various clinical groups are shown in the table. All the HTLV-I positive patients were born in Brazil and half had always lived in Rio de Janeiro.

Clinically the HTLV-I positive patients with a progressive paraparesis often had bladder disturbance and back pain. At examination after a mean duration of disease progression of seven years all had evidence of spasticity in the legs with a paraparesis in 13/15. Only one

HTLV-I is the first human retrovirus to be clearly associated with disease. Initially linked with adult T-cell leukaemia/lymphoma (ATLL)¹ it has also been associated with tropical spastic paraparesis (TSP) particularly in Japan,^{2,3} where it is known as HTLV-I associated myelopathy (HAM), the Caribbean,⁴ and in immigrants from these regions in Europe.⁵⁻⁷ HTLV-I associated with TSP has recently been reported in Africa,^{8,9} but to date there has been only one definitive publication describing patients from the South American continent with HTLV-I associated myelopathy, namely from the coastal strip of Colombia.¹⁰ Paraparesis of obscure origin is, however, common in that continent, particularly in Brazil,¹¹ where Castro *et al*¹² described six patients from Sao Paulo who had a progressive paraparesis and antibodies to HTLV-I in their blood. For these reasons, coupled with the known presence of HTLV-I infection in Rio de Janeiro,^{13,14} we conducted a survey of the HTLV-I status of patients with a variety of neurological conditions, including paraparesis of obscure origin and multiple sclerosis, attending a clinic in Rio de Janeiro.

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Table Demographic data on 46 subjects from Rio de Janeiro examined for presence of HTLV-I

Diagnosis	No of cases	No HTLV-I positive	Mean (range) age (years)	Sex (F/M)	Race (black*/white)	Mean (range) age at onset (years)	Duration of condition (years)
Paraparesis and HTLV-I positive	15	15	49.2 (36-64)	7/8	7/8	41.7 (26-60)	7.0
Paraparesis and HTLV-I negative	12	0	43.0 (31-62)	5/7	4/8	37.8 (23-68)	5.2
Multiple sclerosis	7	1	38.0 (26-53)	5/2	0/7	33	4.8
Motor neuron disease	8	0	45.6	4/4	4/4	42	4.0
Polymyositis	4	0	42.6	3/1	1/3	38	8.0

*Black includes mulatto.

patient, however, was wheelchair bound, and the mean Kurtzke disability score¹⁷ was 4.5. The arms were also often involved with increase in tone and weakness in 4/15 and brisk reflexes in all. Bladder function was abnormal in 14/15 patients, with frequency, urgency or incontinence. Ten of 15 complained of back pain which often radiated down the legs. In contrast to the prominence of these motor findings sensory abnormalities were minor. A third had no abnormality at all on sensory examination, five had a decrease in vibration sense distally in the legs, and the remainder had mild superficial sensory impairment in the legs; three patients had a vague sensory level in the lower thoracic region. The CSF showed a slight pleocytosis and elevated protein content in 5/15 patients. Half the patients had an increase in CSF-IgG concentration. The 12 patients with progressive paraparesis who were HTLV-I negative could not be reliably identified clinically from those who were positive, although they tended to be younger and radicular pain was relatively less common in the HTLV-I negative group (3/12% *v* 10/15% had this symptom).

Discussion

Our study is the first to show that HTLV-I associated myelopathy occurs in Rio de Janeiro and is the cause of paraparesis of unknown origin in about 60% of patients attending an outpatient clinic. Such an observation is not surprising as HTLV-I infection has been detected in Brazilians since 1986 when it was first shown to be present in immigrants from Japan¹⁸ and in high risk groups for HIV infection¹⁴ and, more recently, to be the cause of ATLL in patients resident in Rio de Janeiro.¹⁹ The only other study from Brazil is that of Costa *et al*¹¹ who found six out of 16 patients with chronic myelopathies of undetermined cause in the city of Sao Paulo had HTLV-I antibodies in their blood. The clinical and laboratory features of HTLV-I associated myelopathy in our patients are similar to those in patients from Japan, the Caribbean, and Europe, with two minor exceptions. Firstly, half our patients were of white Caucasian origin, showing that this ethnic group, which comprises over half the total population of Rio de Janeiro, is not immune to the disorder. There are only two case reports^{7,20} from Europe of white patients who did not have specific risk factors (blood transfusion or intravenous drug administration), having HTLV-I associated myelopathy. Secondly, the sexes were equally affected in our series which contrasts markedly

with the female preponderance of HTLV-I associated myelopathy in most other series. The reason for this is obscure.

Risk factors associated with acquisition of HTLV-I infection include blood transfusion.²¹ Five (10%) of our patients had had transfusions, but the incidence of infection in the donors is not known. In a small series of 100 donors from Rio de Janeiro none was positive¹³ but even in endemic areas the overall prevalence is usually only 1-2%; however 6% of patients with Hodgkin's lymphoma in that city did have antibodies to HTLV-I. Intravenous drug addiction is another potential source of infection, but all our patients denied taking drugs by that route and such a method of drug administration is said to be uncommon in Brazil. Breast feeding with infected milk is a potential source of infection²²; all our patients were breast fed, a finding in common with series from the Caribbean, Japan, and in migrants from the West Indies to Europe. All three of the above modes of infection would tend to infect the sexes equally but without more data none is a convincing explanation for the equal sex incidence of HTLV-I associated myelopathy. Finally, sexual transmission of HTLV-I, especially from male to female, is an important factor in the acquisition of infection.²² It is noteworthy that in this study three of the patients had been sailors and one had visited the southern part of Japan where HTLV-I is highly endemic.

None of the patients with clinically definite multiple sclerosis, all of whom were white, had antibodies to HTLV-I. The one patient with a diagnosis of clinically probable MS who was HTLV-I positive had a progressive paraparesis, and the diagnosis depended on a history of visual blurring. This patient might well have been incorrectly classified. Although a number of claims have been made for an association between HTLV-I and MS, the evidence refuting this association is much more compelling.^{23,24} It is more likely that a ubiquitous virus present in the temperate climates induces MS in those with a genetic proclivity. In this regard it is interesting to note that both MS and TSP patients respectively exhibit vigorous immune responses to viruses in general and HTLV-I in particular.^{25,26} Whereas an HLA phenotype association is generally accepted for MS, a specific association between TSP and the HLA-DRb1 chain has recently been described.²⁷ It ought therefore to be possible in Brazil to dissect out the environmental and genetic factors that determine these two diseases. The recent elucidation of the pathogenesis of experimental allergic encephalomyelitis

being determined at the T-cell receptor subgene level and compatible evidence being reported for multiple sclerosis,²⁸ suggest that a thorough elevation of the haplotypic phenotype and T-cell receptor gene repertoire of these patients and their relevance to disease may be more usefully undertaken in this Brazilian population than in populations which do not indigenously have both diseases.

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