Arq Neuropsiquiatr 1995, 53(2): 213-217

HTLV-I ASSOCIATED MYELOPATHY IN PATIENTS FROM BRAZIL AND IRAN

NEUROLOGICAL MANIFESTATIONS AND CEREBROSPINAL FLUID FINDINGS

MARZIA PUCCIONI-SOHLER, **, BERND KITZE*, KLAUS FELGENHAUER**

SUMMARY - We analysed sera and cerebrospinal fluid (CSF) of 20 cases of human T-cell lymphotropic virus type (HTLV-I) associated myelopathy/tropical spastic paraparesis (HAM/TSP) from Brazil and Iran and as controls, 16 Brazilian HTLVI seronegative individuals afflicted with other neurological diseases. It was observed in the HAM/TSP patients that: 1) all had an inflammatory reaction within the central nervous system (CNS); 2) 95% (19/20) showed oligoclonal bands reflecting intrathecal IgG synthesis; 3) 85% (17/20) presented a local synthesis of HTLVI antibodies; 4) 35% (7/20) had a measurable immunoglobulin (Ig) synthesis within the CNS. The CSF parameters of the HAM/TSP were compared with the clinical data (age at onset, duration of disease and disability level). Our data prove that CSF analysis is important for the diagnosis of HAM/TSP. There is no association between the severity of the disease and CSF findings.

KEY WORDS: HTLV-I, HAM/TSP, cerebrospinal fluid, multiple sclerosis.

Mielopatia associada a HTLV-I em pacientes do Brasil e do Irã: manifestações neurológicas e achados no líquido cefalorraquidiano

RESUMO - Foram analisadas amostras de líquido cefalorraquidiano (LCR) e plasma de 20 pacientes com mielopatia associada ao HTLV-I (HAM/TSP) provenientes do Brasil e Irã e como controle, 16 de indivíduos brasileiros soronegativos para HTLV-I acometidos por outras doenças neurológicas (esclerose múltipla, epilepsia idiopática e mielopatia de etiologia desconhecida). Observou-se no grupo de pacientes com HAM/TSP: 1) reação inflamatória no SNC em todos os casos; 2) 95% (19/20) mostravam bandas oligoclonais refletindo síntese intratecal de IgG no SNC; 3)85% (7/20) apresentavam síntese local de anticorpos para HTLV-I; 4)35% (tinham síntese mensurável de imunoglobulinas no SNC. Os parâmetros do LCR dos pacientes com HAM/TSP foram comparados aos dados clínicos (idade de início, duração da doença e grau de incapacidade). Os dados apresentados neste estudo indicam a importancia da analise do LCR para diagnóstico de HAM/TSP. Entretanto nenhuma associação entre a gravidade da doença e os achados do LCR foi demonstrada.

PALAVRAS-CHAVE: HTLV-I, mielopatia, HAM/TSP, líquido cefalorraquidiano, esclerose múltipla.

Since the last century, cases of spastic paraparesis with unknown etiology were reported in tropical countries. The presence of HTLV-I antibodies was demonstrated in serum and CSF of patients with this myelopathy in tropical areas and Japan[3,14]. In the developing countries, where the HTLV-I infection is endemic, HTLV-I associated myelopathy may be difficult to be recognized due to some diagnostic deficiences. Moreover, the clinical course may be similar to other chronic spinal cord

* Klinik und Poliklinik für Neurologie der Georg-August-Universität, Göttingen, Germany; ** Serviço de Neurologia do Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro (HUCFF/ UFRJ), CNPq/CAPES, Brasil, DAAD. Aceite: 4-novembro-1994.

Dra. Marzia Puccioni-Sohler - R. Francisco Sá, 26/1201 - 22080-010 Rio de Janeiro RJ - Brasil. Fax: (55)(21) 5211175.

diseases as neurolues, myelitis, spinal form of multiple sclerosis (MS), compressive lesions, degenerative disorders and other myelopathies of unknown etiology[11].

Here, we report the importance of the CSF analysis for the diagnosis of HTLV-I associated myelopathy and we correlate the neurological manifestations of HTLV-I associated myelopathy with the CSF analysis in an effort to determine a relationship between these parameters and the severity of the disease.

PATIENTS AND METHODS

Specimens of CSF and serum were obtained from 18 (14 females) Brazilian patients (age range 37 to 69 years) seen at Neurologic Clinic of the Clementino Fraga Filho Hospital, Federal University of Rio de Janeiro, Brazil and two (1 female) Iranian immigrants to Germany (age 32 and 63 years) seen at Neurologic Clinic of the Göttingen University, Germany. The patients fulfilled the criteria for HTLV-I associated myelopathy[15].

Gait disability scale was used as a parameter of incapacity since this disturbance was the main clinical problem. The gait disability scale was defined in six groups and is adapted from the incapacity scale for MS patients (Hauser et al.[6]): B. normal gait, no fatigue; C. normal gait but with fatigue; D. abnormal gait but unaided; E. gait aided with one stick; F. gait aided with bilateral support; G. wheel chair.

As controls, serum and CSF samples were collected from 16 Brazilian patients (14 females; age range 15 to 45 years) seen at the same Hospital in Rio de Janeiro. The control group consisted of: six cases with spinal MS (Poser et al. criteria [15]), three myelopathies of unknown etiology and seven idiopathic epilepsy cases (non-inflammatory control).

Table 1. Clinical data of 20 HAM/TSP cases.

No. Case	Age/Sex	Race	Duration of disease (years)	Risk Group	Disability
1*	63/F	W	15	BT	5
2	52/F	W	15	U	3
3	54/F	M	14	BT	3
4	37/F	B	10	U	4
5	63/F	W	8	BT/FH	3
6	39/F	M	8	FH	4
7	42/F	W	8	BT	4
8*	32/M	W	7	U	2
9	69/M	B	7	FH	2
10	57/F	W	7	U	1
11	59/F	M	6	BT	4
12	61/F	M	5	U	2
13	43/M	W	5	U	4
14	57/F	B	5	FH	4
15	50/F	W	5	U	2
16	40/M	M	5	U	2
17	56/F	M	4	U	2
18	62/M	W	2	U	5
19	41/F	W	1	U	2
20	37/F	M	1	FH	1

F, female; M, male; W, white; B, black; M, mulatto; BT, blood transfusion; U, unknown; FH, familial history; * Iranian patients. Disability: 1, normal; 2, unaided; 3, aided with one stick; 4, aided with bilateral support; 5, wheel chair.

Laboratory studies

A commercial enzyme immunoassay (EIA) (Du Pont, Wilmington, DE, USA) was used to screen for HTLV-I antibodies in serum samples. Radio-immunoprecipitation assay (RIPA) was done to confirm the results on all specimens. The precipitation of core as well as envelope viral proteins by the diluted serum samples was considered positive.

CSF analysis (including cell count, proteins and glucose) were done in all patients. Albumin and immunoglobulins in serum and CSF were determined by nephelometry. The index for the synthesis of IgG, IgA and IgM in CSF was calculated according to the formula by Reiber and Lange[16]. In addition, isoelectric focusing and silver-stain was performed to detect oligoclonal IgG bands. The presence of bands restricted in CSF or with two or more bands in CSF, not found in serum, were considered as intrathecal IgG production[10].

Intrathecal synthesis of HTLVI IgG antibodies was evaluated quantitatively by the specific antibody index (AI) through the ELISA method. MT-2 cells (10^6 per well) were spun down in EIA plates (NUNC). After adherence washing medium was removed and cells were fixed with methanol. Otherwise ELISA was performed as described by Reiber and Lange[16]. Values higher than 1.5 were established as positive.

RESULTS

The mean age of onset of the symptoms was 43 years (range, 27 to 62 years), with a mean

duration of 7.4 years (range, 1 to 15 years). The progression of disease was different in our 20 HTLV-I associated myelopathy patients (Table 1).

Table 2 summarizes the CSF data. A mild mononuclear CSF pleocytosis (4-8 cells/mm3) was observed in 30% of patients, intrathecal synthesis of IgG in 35%, IgA in 10% and IgM in 5%. The blood-CSF-barrier function was abnormal in 30%. All Brazilian patients and one Iranian patient had oligoclonal IgG bands in CSF (95%), reflecting intrathecal IgG synthesis. The HTLVI antibody specificity index was elevated in 85% of the patients. One case with negative HTLVI AI had increased IgG, IgA, IgM index, one had IgG and IgA index and the other had no measurable Ig synthesis. All these three patients had oligoclonal IgG in CSF. The figure 1 shows the correlation between the clinical and CSF findings.

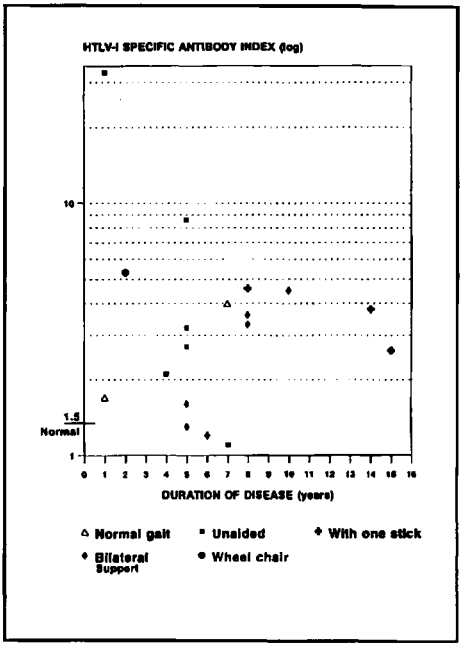

Fig 1. Relation between antibody specificity indice (AI) and duration of disease.

COMMENTS

In this study no evident relationship was demonstrated between age at onset, duration of disease, gait disability, intrathecal IgG and HTLVI IgG synthesis in CSF of 20 HAM/TSP patients. We have however found evidence for a chronic inflammatory myelopathy in all patients tested.

Table 2. CSF findings in 20 HAM/TSP and 16 controls.

	HAM/TSP	CONTROL		
		MUE	MS	EPILEPSY
	n=20	n=3	n=6	n=7
Oligoclonal bands	19	0	6	0
.CSF restricted	11	0	6	0
.CSF restricted with additional identical band in CSF and serum	8	0	0	0
HTLVI - antibodies synthesis	17	0	0	0
Mild pleocytosis (>4 cells/µl)	6	0	2	2
* Intrathecal IgG synthesis (%)	7	0	6	0
* Intrathecal IgA synthesis (%)	2	0	0	0
* Intrathecal IgM synthesis (%)	1	0	0	0
Impaired blood barrier	6	0	0	0

MUE, myelopathy of unknown etiology;* IgG loc>0

The age at onset of our 20 HTLV-I associated myelopathy patients was similar to other reports[18]. We have seen no correlation between a quick course of disease and the earlier age at onset as it was described to some HTLV-I associated myelopathy patients[8].

A variation in the progression of paraparesis was observed in some cases. One patient had a normal gait after seven years. A rapid progression (two years of disease and wheelchair bound) was observed in one patient with concomitant leprosy . A quick course was also found in the group of patients that needed bilateral support (two of these had blood transfusions history). Conversely, after 14 and 15 years of having their symptoms, two other patients could walk aided only with one stick. Both had blood transfusion history. According to the literature the majority of our patients had a slowly evolution[18].

In contrast to Sheremata et al.[18] in which five cases with highest IgG index progressed quickly to a worse incapacity, we did not observe in our patients this association. The CSF analysis of the three control patients with myelopathy of unknown etiology and the seven with idiopathic epilepsy was normal. All MS cases had an inflammatory reaction in CSF, but without an intrathecal IgA, IgM or HTLV-I antibody synthesis.

The presence of oligoclonal bands was the most sensitive parameter to detect a humoral immune response within the central nervous system (95% of cases). It is found in other neurological diseases as MS, viral and nonviral infections of the nervous system[4,19]. It has been reported that the oligoclonal bands are found constant during the course of HAM/TSP as well in other chronic neurological inflammatory diseases[2]. In general, we observed a higher frequency of oligoclonal bands (reflecting IgG intrathecal production) than reported before, which may be related to our sensitive method.

Anti-HTLVI antibodies (ELISA and RIPA) were found in serum of all HAM/TSP patients. The HTLVI IgG synthesis within the CNS was evaluated by the HTLVI specific antibody index AI[16].

Increased HTLVI AI was observed in 85% of our HAM/TSP patients but not in the controls (MS, myelopathy of unknown etiology and epilepsy). The three HAM/TSP with a negative HTLVI AI had also an inflammatory reaction in the CSF. Oligoclonal IgG bands were found in all negative HTLV-I AI, elevated intrathecal IgG title in two of these, IgA in two and IgM in one, who had blood transfusion history and a quick progression to bilateral support. It has been reported not only that HTLV-I IgG is present in serum and CSF of HTLV-I associated myelopathy patients, but also IgM[5]. IgG and IgM oligoclonal bands directed against HTLV-I have been described[9,12]. The detection of viral specific IgG in CSF seems to be related to the presence of the virus in central nervous system. Higher frequency of positivity of viral specific IgM in CSF has been found in HAM/TSP patients with blood tranfusion history[13]. We could not find a relation between the specific antibody index for intrathecal anti-HTLV-I antibody synthesis and the time of disease or with the severity of the gait disturbance.

In summary, our data suggest that the CSF analysis has a great value in the diagnosis of HAM/TSP. We have observed an inflammatory reaction in the CSF of all patients. This is corroborated by the histopathological findings of a chronic inflammatory reaction with demyelization in the spinal cord and brain of HAM/TSP[7]. The synthesis of HTLV-I antibodies within CNS contributed to the diagnosis of HAM/TSP. Although more extensive studies will be necessary to elucidate the significance of these antibodies and other findings like intrathecal synthesis of IgA and IgM in the pathogenesis of HAM/TSP. In contrast to some neuropathological studies in which a severe inflammation has been found in the cases of short time disease[5], CSF findings were not related with the duration of HAM/TSP or the clinical course. The variability of progression observed in our patients may be associated with other factors (genetics, environment or virulence) that could contribute to the course of the disease.

Acknowledgement - We thank Prof. Dr. H.O. Reiber for his helpfull support at the Neurochemistry Labor von der Klinik und Poliklinik für Neurologie der Georg-August-Universität, Göttingen, Germany.

REFERENCES

1. Cavalcanti M, Ferreira O, Puccioni M, Novis S, Schechter M. HTLV-I associated neurologic manifestations in four generations of a Brazilian family. J AIDS 1993, 6:213-217.
2. Ceroni M, Piccardo P, Rodgers-Johnson P et al. Intrathecal synthesis of IgG antibodies to HTLV-I supports an etiological role for HTLV-I in tropical spastic paraparesis. Ann Neurol 1988, 23(Suppl):S188-S191.
3. Gessain A, Barin F, Vernant JC et al. Antibodies to human T-lymphotropic virus type I in patients with tropical spastic paraparesis. Lancet 1985, 2:407-410.
4. Gessain A, Caudie C, Gout O et al. Intrathecal synthesis of antibodies to human T lymphotropic virus type I and the presence of oligoclonal bands in the cerebrospinal fluid of patients with endemic tropical spastic paraparesis. J Inf Dis 1988, 6:1226-1234.
5. Gessain A, Gout O. Chronic myelopathy associated with human T -lymphotropic virus type I (HTLV-I). Ann Intern Med 1992, 117:933-946.
6. Hauser SL, Dawson DM, Lehrich JR et al. Intensive immunossupression in progressive multiple sclerosis. N Engl J Med 1983, 308:173-180.
7. Kitze B, Turner RW, Burchhardt M, Poser S, Hunsmann G, Weber T. Differential diagnosis of HTLV-I associated myelopathy and multiple sclerosis in Iranian patients. Clin Investig 1992, 70:1013-1018..
8. Kuroda Y, Fujiyama F, Nagugumo F. Analysis of factors of relevance to rapid clinical progression in HTLV-I-associated myelopathy. J Neurol Sci 1991, 105:61-66
9. Iwasaki Y. Pathology of chronic myelopathy associated with HTLVI infection (HAM/TSP). J Neurol Sci 1990, 96:103-123.
10. Link H, Cruz M, Gessain A et al. Chronic progressive myelopathy associated with HTLVI: oligoclonal bands and anti-HTLVI IgG antibodies in cerebrospinal fluid and serum. Neurology 1989, 39:1566-1571.
11. Marti-Fabregas J, Martinez JM, Illa I, Escartin A. Myelopathy of unknown etiology. Acta Neurol Scand 1989, 80:455-460.
12. McLean BN, Rudge P, Thompson EJ. Viral specific IgG and IgM antibodies in the CSF of patients with tropical spastic paraparesis. J Neurol 1989, 236: 351-352.
13. Nagasato K, Nakamura T, Ohishi K et al. Active production of anti-human T-lymphotropic virus type I (HTLV-I) IgM antibody in HTLV-I-associated myelopathy. J Neuroimmunol 1991, 32:105-109.
14. Osame M, Usuku K, Izumo S et al. HTLV-I associated myelopathy, a new clinical entity. Lancet 1986, 1:1031-1032.
15. Poser CM, Paty DW, Scheinberg L et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983, 13:227-231.
16. Reiber H, Lange P. Quantification of virus specific antibodies in cerebrospinal fluid and serum: sensitive and specific detection of antibody synthesis in brain. Clin Chem 1991, 37:1153-1160.
17. Roman G, Roman LN, Osame M. Human T lymphotropic virus type I neurotropism. Prog Med Virol. Basel: Karger, 1990; 37: 190-210.
18. Sheremata WA, Berger JR, Harrington WJ, Ayyar R, Staford M, DeFreitas E. Human T lymphotropic virus type-I associated myelopathy. Arch Neurol 1992, 49:1113-1118.
19. Spina-Franca A, Livramento JA, Machado LR et al. HTLV-I antibodies in serum and cerebrospinal fluid in tropical spastic paraparesis in Brazil. Arq Neuropsiquiatr 1990, 48:441-447.