Acta Neurol Scand 2000: 101: 405–412
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ACTA NEUROLOGICA
SCANDINAVICA
ISSN 0001-6314

Spinocerebellar syndrome in patients infected with human T-lymphotropic virus types I and II (HTLV-I/HTLV-II): report of 3 cases from Panama

Castillo LC, Gracia F, Román GC, Levine P, Reeves WC, Kaplan J. Spinocerebellar syndrome in patients infected with human T-lymphotropic virus types I and II (HTLV-I/HTLV-II): report of 3 cases from Panama.
Acta Neurol Scand 2000: 101: 405–412. © Munksgaard 2000.

Cerebellar symptoms at onset are unusual in HTLV-I/II-associated tropical spastic paraparesis (TSP). A prospective study of neurological disorders in Panama (1985–1990) revealed 13 patients with TSP and 3 with HTLV-I/II-associated spinocerebellar syndrome (HSCS) presenting at onset loss of balance, wide-based stance and gait, truncal instability, and mild leg ataxia (vermian cerebellar syndrome), with absent upper limb dysmetria but with postural tremor, downbeat nystagmus, and dysarthria. In 4–5 years, spinal cord manifestations of TSP developed, including spastic paraparesis, pyramidal signs, bladder and sphincter disturbances. Two patients were infected with HTLV-I and another one, a Guaymi Amerindian woman, with HTLV-II. Magnetic resonance imaging (MRI) demonstrated cerebellar atrophy involving predominantly the superior vermis. Mild axonal peripheral neuropathy in the lower limbs, dorsal column involvement and inflammatory myopathy were found by neurophysiology studies. There are 14 similar cases reported in Japan and Canada, but to our knowledge these are the first documented cases of HSCS in the tropics. A cerebellar syndrome constitutes another form of presentation of HTLV-I/II infection of the nervous system.

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Key words: human retroviruses; HTLV-I; HTLV-II; cerebellar disorders, tropical spastic paraparesis; magnetic resonance imaging; Panama

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Accepted for publication February 8, 2000

The first human retrovirus, human T-lymphotropic virus type I (HTLV-I), is considered the etiologic agent of both adult T-cell leukemia/lymphoma (ATLL) and HTLV-I myelopathy. The latter is a chronic myelitis currently denominated HTLV-I-associated myelopathy (HAM) in Japan (1) and HTLV-I-associated tropical spastic paraparesis (TSP) elsewhere (2–5). ATLL and HAM/TSP occur predominantly in southern Japan and in areas of the Caribbean and South America where HTLV-I seroprevalence ranges from 1% to 15% (6). In Panama, a traditional region of transit with a population characterized by high degree of racial mixture, HTLV-I seroprevalence ranges from 0.2% to 2% (7). Levine et al. (8) demonstrated the occurrence of HTLV-I-associated ATLL in Panama, and Gracia et al. (9), in a prospective evaluation of adult neurological patients, concluded that HTLV-I-associated TSP is the most common cause of non-compressive spastic paraparesis in Panama.

Throughout the Americas, TSP is also the main clinical manifestation of HTLV-I infection of the nervous system (10). Nonetheless, anterior-horn cell involvement, cerebral white matter and eye lesions,

cerebral vasculitis, peripheral neuropathy, sicca syndrome, polymyositis and myopathy have been reported with HTLV-I infection (6, 10, 11–17). In addition to the primary involvement of the spinal cord, neuropathologic examination reveals inflammatory lesions in the cerebellum, as well as in the brain, medulla and pons (18–20). HTLV-I tax (pX) gene expression in the inflammatory lesions has been demonstrated and appears to be an important factor in the pathogenesis of the neural lesions (19–21).

We studied 3 Panamanian patients with a cerebellar syndrome that was followed years later by more characteristic manifestations of TSP, following a pattern clinically consistent with a spinocerebellar syndrome. Two of these patients were found to be infected with HTLV-I and another one, a Guaymi Amerindian woman, with HTLV-II. The purpose of this report is to describe the clinical picture, the magnetic resonance imaging (MRI) alterations in the cerebellum, and the clinical neurophysiology studies in these patients. We reviewed the literature and concluded that prominent cerebellar signs may occur at onset as part of the clinical spectrum of HTLV-associated neurological diseases.

Material and methods

Patients

In 1985, a registry of patients with chronic idiopathic and degenerative neurological diseases was established in 4 tertiary public and private hospitals in the metropolitan area of Panama City, Panama. These hospitals also receive referrals from rural areas and cover about 81% of the Panamanian population. All adult neurological patients admitted for the first time between 1985–1990 were screened for HTLV-I/II infection.

Serological procedures

Serum samples were screened at the Gorgas Memorial Laboratory in Panama using the HTLV-I enzyme-linked immunosorbent assay (ELISA) (Dupont de Nemours, Wilmington, DE, USA) and confirmed by Western blot (WB) and radioimmunoprecipitation assay (RIPA) performed at the Centers for Disease Control and Prevention (CDC) in Atlanta, GA, USA. Seropositivity for HTLV-I and HTLV-II was defined by the United States Public Health Service (USPHS) criteria (22). Seropositive specimens underwent further testing by type-specific synthetic peptide serology to differentiate HTLV-I from HTLV-II infection (23). The polymerase chain reaction (PCR) method was used to amplify DNA obtained from peripheral blood lymphocytes (PBLs) of Patient 3, using specific primers for different regions of the HTLV-I and HTLV-II genomes.

Case descriptions

Patient 1

This 52-year-old teacher, a white woman from Chitre, an urban village in central Panama, was admitted to the hospital in June 1985 with a 2-year history of loss of balance, unsteadiness of gait, frequent falls, and tremor of upper limbs which hindered her handwriting. She also complained of plantar paresthesiae, urinary urgency, and occasional incontinence. The patient denied alcohol consumption. Her past medical history revealed 3 normal deliveries, no abortions, appendectomy at age 30, and hysterectomy at age 45 without blood transfusions. There was no family history of neurological disorders. General physical examination was normal. Positive findings on neurological examination included ataxic gait with clumsiness of leg movements, as well as postural tremor and loss of manual dexterity. Romberg test was negative. Remaining examination including higher cortical functions, cranial nerves, strength, muscle tone, and deep tendon reflexes were all normal. Plantar response was normal on the left and questionable on the right. Sensory exam was completely normal. Cerebrospinal fluid (CSF) examination showed 17 leukocytes/mm^3 with 90% mononuclear cells, protein 67 mg/dl, glucose 53 mg/dl, and negative VDRL, cytology and cultures. ELISA and WB tests were positive for HTLV-I/II in serum and CSF. Synthetic peptide serologic testing confirmed HTLV-I infection. Computerized tomography (CT) scan of the brain showed only slight frontal cortical atrophy.

Three years later, in March of 1988, the patient complained of blurred vision, leg weakness, urinary incontinence, and constipation. Neurological examination revealed again a slow and staggering wide-based gait with poor balance but Romberg test remained negative. There was no dysmetria, dysdiadochokinesia, nystagmus, or dysarthria; a slight tremor of fingers and hands persisted. New findings on neurological examination included muscle weakness involving mainly deltoids (4/5), iliopsoas muscles (4/5), and feet dorsiflexors (3/5 on the right, 4/5 on the left), with normal tone and slight distal wasting in the 4 extremities, with rare fasciculations in the legs. Deep tendon reflexes were brisk on the legs, without clonus but with bilateral Babinski sign.

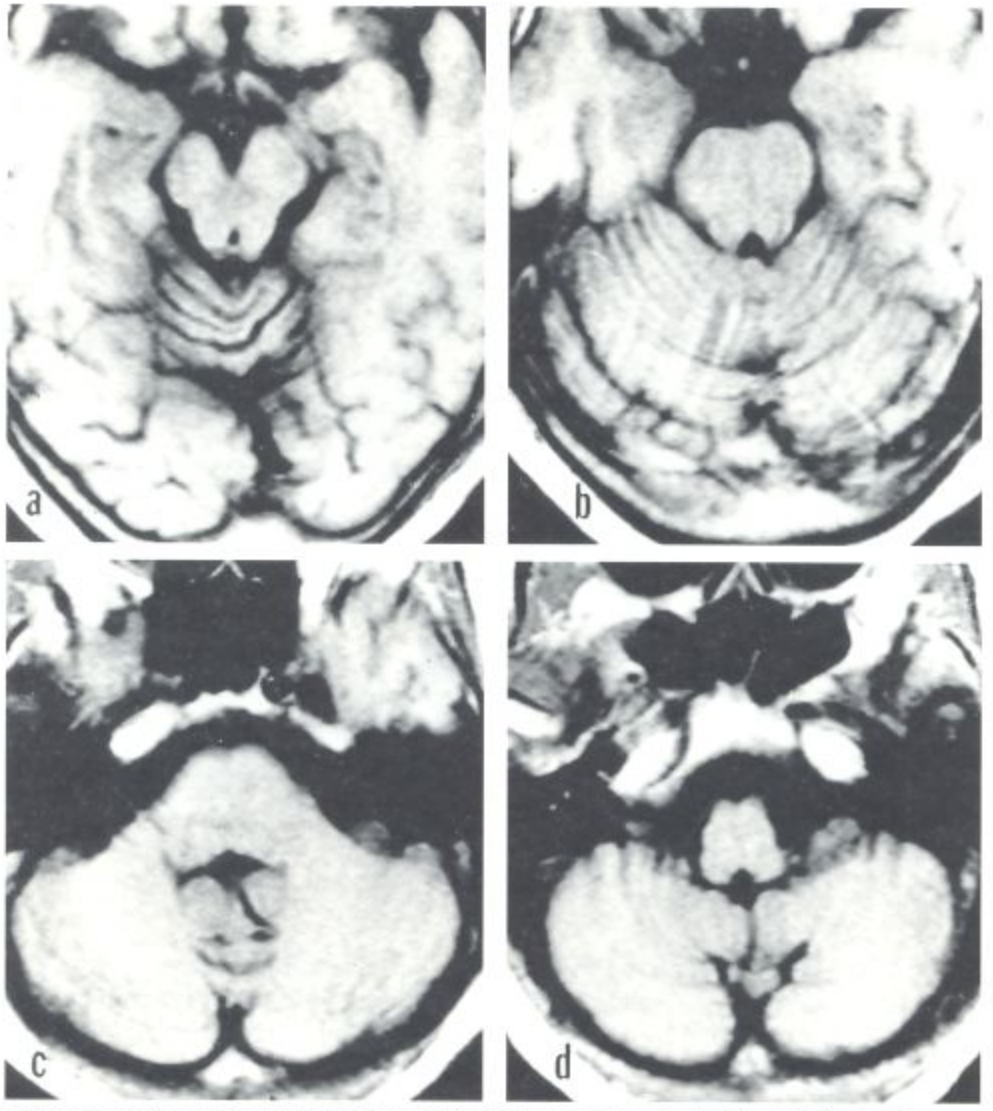

Fig. 1. Axial T_1-weighed proton density MRI (TE 16, TR 545, SE technique) of Patient 2 illustrating atrophy of superior vermis with normal mesencephalon (a). At upper pontine level (b) slight bilateral atrophy of anterior lobe folia manifested by widening of cerebellar fissures is apparent. At mid-pontine level (c) the appearance of cerebellar hemispheres, middle cerebellar peduncles, and fourth ventricle is normal. At upper medullary level (d) widening of anterior cerebellar fissures is present.

By August of 1990 the gait was completely unbalanced and she needed a walker to ambulate. Neurological examination was otherwise unchanged. Serum CPK was normal (76 IU/l), CSF had 40 mg/dl of protein with 3 cells/mm^3. Visual and auditory evoked potentials (VEP and AEP) were normal. Needle electromyography (EMG) showed slight to moderate chronic denervation of distal leg muscles bilaterally. Motor and sensory nerve conduction velocities (NCV), H reflex and F responses were all normal. Lower limb somatosensory evoked potentials (SEP) showed considerable delay of the p40 waves.

Patient 2

A 46-year-old mestizo woman from Colón, a city in the Atlantic Coast of Panama, was admitted in August 1987, with a 1-year history of unsteadiness of gait. She had a past history of 10 deliveries and 1 abortion prior to a hysterectomy in 1979, without blood transfusions. The patient denied alcohol consumption and there was no neurological disease in the family. General physical examination was normal. Positive findings on neurological examination included bilateral gaze-evoked horizontal nystagmus and ataxic gait. Romberg test was positive, gait was unsteady and wide-based. Coordination and motor examination of the upper limbs were normal. The remainder of the examination, including higher cortical functions, other cranial nerves, strength, muscle tone, and deep tendon reflexes were all normal. Plantar responses were flexor and clonus was not elicited. Sensory exam was completely normal. Blood tests were noncontributory. CSF

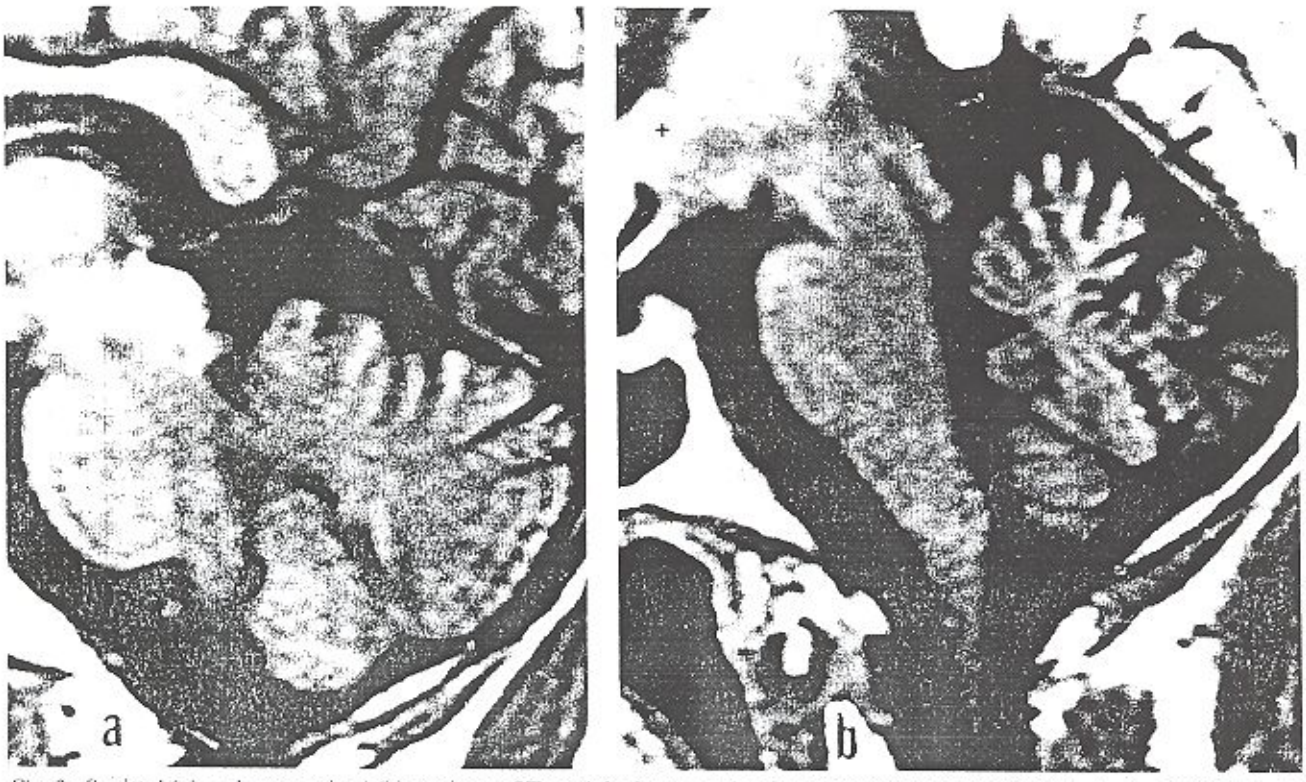

Fig. 2. Sagittal (a) and parasagittal (b) sections of T_1-weighed proton density MRI (TE 20, TR 520, SE technique) of Patient 2 at posterior fossa level demonstrating extensive atrophy of superior cerebellar vermis with narrowing of folia. Widening of fissura prima and to a lesser extent of horizontal and prepyramidal fissures is apparent. Pons and mesencephalon appear normal in these views.

examination showed no cells, protein 63 mg/dl, negative VDRL, and presence of oligoclonal bands. CSF cytology and cultures were negative. Brain CT scan, myelogram, VEP, AEP and electroencephalogram (EEG) were all normal. SEPs showed delayed responses on lower limb stimulation. ELISA and WB tests were positive for HTLV-I/II in serum; CSF was ELISA-positive but unconfirmed by WB. Synthetic peptide serology confirmed HTLV-I infection.

In January 1989, VEPs were found to be abnormal at a 30° angle, with normal responses at 15°. The patient was readmitted in April of 1990. Gait had worsened and she complained of blurred vision, weakness, numbness and pain of the legs, urinary urgency, incontinence and constipation. Neurological examination showed marked instability, wavering and unsteadiness when standing with the feet less than 10 cms apart, aggravated by closing the eyes. Gait was slow, wide-based, unsteady, but it also had a myopathic appearance with pelvic weakness. Downbeat nystagmus was present in neutral gaze position increasing with upward and lateral gaze. In addition, there was a moderately severe paraparesis with weakness of flexion and abduction of the thighs (3/5), hyperreflexia and bilateral Babinski sign without clonus, and slightly increased tone; sensory examination was completely normal. Laboratory tests were normal except for a CPK of 596 IU/l (*N*: 33–196). NCVs were normal, except for mild slowing of the left posterior tibial nerve. EMG showed bilateral polyphasics in quadriceps, gastrocnemius and extensor digitorum brevis. VEPs had worsened with absence of the P100 waves. Muscle biopsy of the right quadriceps was reportedly normal.

MRI of the head and cervical cord was performed in May of 1993. Significant atrophy of the superior cerebellar vermis was demonstrated (Figs 1, 2) as characterized by widening of the cerebellar folia with normal appearance of the pons and brachium pontis (Fig. 1c). Age-related, minimal, frontal white-matter hyperintensities were seen on T_2 spin-echo images. Cervical spinal cord MRI was normal. No abnormal enhancement was seen after gadolinium injection and there were no lesions suggestive of multiple sclerosis.

Patient 3

This 51-year-old Guaymi Amerindian woman from Río de Jesús, a small village in the Veraguas region of Panama, was admitted in

December of 1984 with a history of vertiginous rotatory sensations induced by head movements, progressive unsteadiness of gait, dysarthria, and intermittent diplopia. She had history of 5 pregnancies, 4 spontaneous abortions, and of having received a blood transfusion during her first delivery. There was no family history of neurological disorders and no alcohol consumption. General physical examination was unremarkable. Positive findings on neurological examination included scanned dysarthric speech, mild horizontal nystagmus, wide-based gait with unsteadiness on turning, dysdiadochokinesia, and limb dysmetria more severe in the arms than in the legs. Deep tendon reflexes were brisk with flexor plantar responses. Laboratory examinations were normal. A brain CT revealed diffuse cerebellar atrophy, without features of olivo-pontocerebellar atrophy (OPCA).

Repeated examination in 1988 noticed presence of paraparesis, urinary urgency, incontinence, and constipation. She also had intermittent dysphagia and the dysarthria had worsened. Nystagmus was mild and there was no diplopia. Gait was unsteady, ataxic and broad based. Muscle tone was normal. Reflexes were brisk in the legs, without clonus or Babinski sign. Marked dysmetria was present on finger-to-nose and ankle-to-knee tests but there was no tremor of fingers or hands. CSF had 40 mg/dl of protein and 2 cells/mm^3. Serum was positive for HTLV-I/II antibodies by ELISA and WB, and PCR amplification of DNA from PBLs confirmed HTLV-II infection.

The patient was last examined in October of 1990. At that time, she was able to ambulate only with support or using a walker; gait was slow and staggering, with irregular, ataxic steps. Her voice was slow, slurred, and unintelligible. There was upbeat nystagmus on upward gaze and slight horizontal nystagmus. Reflexes were brisk in the legs but without clonus or Babinski sign.

Discussion

The clinical presentation of the patients reported here illustrates the development of a cerebellar syndrome as the initial manifestation of HTLV infection. With time, these patients evolved towards the more characteristic neurological manifestations of HTLV myelopathy, indicating a rostral-caudal progression of the disease in a pattern clinically consistent with a spinocerebellar syndrome. Review of the literature revealed 14 previous reports (Table 1) of patients with HTLV-I or II presenting with cerebellar signs at onset. In Japan, Iwasaki et al. (24) and Kira et al. (25) first described a spinocerebellar syndrome clinically similar to the one we report here in patients with HTLV-I infection. More recently, Oger et al. (26) informed the case of a 52-year-old Caucasian woman from British Columbia, Canada, with HTLV-II infection and a chronic spinocerebellar syndrome. We were unable to find previously published instances of this clinical syndrome in the tropics.

The first 2 patients reported here presented with a typical midline or vermian cerebellar syndrome characterized clinically by loss of balance, wide-based stance and gait, slight instability of the trunk, and mild ataxia of the legs, in the absence of dysmetria of the upper limbs, dysarthria or pyramidal signs. These symptoms and signs are very similar to those described in patients with alcoholic cerebellar degeneration (27). Also, Patient 1 had postural tremor made worse in certain positions, severe enough to interfere with hand-writing. A similar postural tremor has also been described in patients with alcohol-induced lesions of the cerebellar vermis and anterior lobes (27). Downbeat nystagmus, present in Patient 2, has been reported with alcoholic cerebellar degeneration (28), although its presence usually suggests either Arnold Chiari malformation or OPCA. The absence of family history, corneal pigmentation

Table 1 Reported cases of HTLV-I/II infection with cerebellar signs at onset

Case no.	Authors/year	Age/sex at onset	Cerebellar signs	Spinal signs	Retrovirus
1	Iwasaki et al. 1989 [24]	64/W	Tremor, unsteady gait, saccadic eye movements. MRI: WM lesions	Paraparesis	HTLV-I
2–9	Kira et al. 1993 [25]	24–70 years/ 3M–5W	Chronic progressive cerebellar ataxia MRI: cerebellar atrophy	Babinski, hyperreflexia LE	HTLV-I
10	Iwanaga & Mori 1993 [51]	37/W	Pendular eye movements	Paraplegia	HTLV-I
11	Sato et al. 1994 [52]	55/M	Limb ataxia	Paraparesis	HTLV-I
12	Waragai et al. 1995 [53]	59/W	Downbeat nystagmus ocular hypermetria MRI: vermis atrophy	Paraparesis	HTLV-I
13	Oger et al. 1995 [26]	52/W	Chronic progressive cerebellar ataxia	Paraparesis	HTLV-II
14	Fujiki et al. 1999 [54]	72/W	Unsteady gait, truncal ataxia, nystagmus	Paraparesis	HTLV-I
15	Castillo et al. 2000	50/W	Unsteady gait, leg ataxia, finger tremor	Paraparesis	HTLV-I
16	Castillo et al. 2000	45/W	Unsteady gait, truncal ataxia, downbeat nystagmus MRI: vermis atrophy	Paraparesis	HTLV-I
17	Castillo et al. 2000	51/W	Unsteady gait, truncal ataxia, dysarthria, limb dysmetria, nystagmus	Paraparesis	HTLV-II

LE = lower extremities; M = man; MRI = magnetic resonance imaging of the brain; W = woman; WM = white matter.

(Kayser–Fleischer ring), liver abnormalities, flapping tremor, choreiform movements of the face and hands, dysarthria, dysphagia, and rigidity militate against a diagnosis of Wilson's disease or hepatolenticular degeneration (29).

Kira et al. (25), demonstrated by MRI atrophy of cerebellum and brainstem in patients with HTLV-I-associated spinocerebellar syndrome (HSCS) in Japan. We also found atrophy of the folia of the superior cerebellar vermis in Patient 2, with widening of the fissure prima, horizontal and prepyramidal fissures, but without significant pontine or brainstem atrophy. These features are different from those described in MRI of patients with OPCA, striatonigral degeneration, multiple system atrophy and other forms of late-onset cerebellar degeneration (30–33). Japanese patients with HSCS presented on MRI a significantly higher number of cerebral white matter lesions than a control group. Such lesions in our second patient were considered to be within normal range for age. MRI lesions of the white matter in the elderly are probably of vascular nature (34), but in the absence of neuropathologic studies, the nature and distribution of these lesions in patients with HSCS remain unclear.

The combination of cerebellar and pyramidal signs, incontinence, paresthesiae, and tremor, as well as the presence of nystagmus and oligoclonal bands in Patient 2, raised the diagnostic possibility of multiple sclerosis (MS). However, the clinical features, absence of significant white matter lesions on imaging studies, presence of electrophysiological alterations of peripheral nerves, elevation of CPK, and the positive HTLV-I serology excluded the diagnosis of MS, according to prevailing criteria (35). Although extraspinal symptoms are relatively rare in HAM/TSP, alterations of ocular pursuit were reported by Arimura et al. (36) in 11/22 patients studied by electronystagmography. Cerebellar signs, in particular end-point intention tremor and mild dysmetria, have been noted in patients with TSP with frequencies ranging from 7% in Jamaica (37), 14% in Tumaco, Colombia (38), to 19% in the Seychelles Islands (39). In cases of HAM/TSP evaluated at advanced stages, however, the cerebellar syndrome may pass unnoticed because of the severity of the weakness and spasticity resulting from the chronic myelopathy.

The neurophysiological alterations found in the present cases are similar to those previously described in HAM/TSP (40) including subclinical prolongation of SEPs in the lower limbs suggestive of involvement of the dorsal columns, in particular of the fasciculus gracilis (13). These patients also had an asymmetrical peripheral neuropathy of the lower limbs as previously reported (13, 17). In addition, EMG and laboratory findings in the first two patients suggested the coexistence of polymyositis and anterior horn cell lesions (12, 13, 15).

HTLV-II is endemic in Amerindian tribes, in isolated populations in Mongolia and North Africa, and in intravenous drug users in Europe and the USA. HTLV-II has been reported in association with rare cases of hairy-cell leukemia and large-cell lymphoma, as well as in a few cases of chronic myelopathy resembling either TSP (41–43) or tropical ataxic neuropathy (44, 45). A familial form of OPCA has been associated with HTLV-II infection in Amerindians from New Mexico (46). In Panama, HTLV-II infection is restricted almost exclusively to the Guaymi Indians (47) and we confirmed a retroviral infection with HTLV-II in our third patient, a Guaymi Amerindian woman. The clinical and radiological features in this patient were consistent with global cerebellar dysfunction without evidence of OPCA. No relatives of Patient 3 were found to be affected by a similar disorder. Moreover, in a careful long-term neurological evaluation of Guaymi Indian tribes by the same group of neurologists we have recently detected HLTV-II-associated sensory myeloneuropathy (45) but no other instances of spinocerebellar syndrome.

In the current study, 13 incident cases of TSP were ascertained in Panama from 1985 to 1990 for a period prevalence of 1.6 cases per million inhabitants per year. The finding of 3 cases of HTLV-I/II-associated spinocerebellar syndrome (HSCS) during this same time period appears unusually high when compared with the rarity of HSCS reported from areas endemic for HTLV-I/II infection. This dearth of cases may be due to the mandatory exclusion of cerebellar signs in the current diagnostic criteria of HAM/TSP (48). This is owing to the need to exclude cases of MS occurring in HTLV-I/II carriers. However, it is conceivable that some previously reported cases of HTLV-associated MS (49, 50) could have been instances of the spinocerebellar syndrome we describe here. In conclusion, it is recommended to explore the possibility of HTLV-I or HTLV-II infection in patients with cerebellar syndromes of unknown etiology.

Acknowledgements

The cooperation of the Centro Médico Paitilla, Panama City, Panama, in performing the MRI studies is gratefully acknowledged.

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