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Tropical Spastic Paraparesis/ HTLV-I Associated Myelopathy

Etiology and Clinical Spectrum

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Abstract

In 1985 we had the first indication that human T-cell lymphotropic virus (HTLV-I) was the possible etiological agent of a chronic myelopathy that seemed to be peculiar to the tropics and that is now known as endemic tropical spastic paraparesis (TSP). IgG antibodies to HTLV-I were found in serum and cerebrospinal fluid of patients from Jamaica, Colombia, Martinique, and shortly after in southern Japan, where the disease is called HTLV-I-associated myelopathy (HAM). The HTLV-I seropositivity was first determined by enzyme-linked immunoassay and confirmed by western immunoblot and in the cerebrospinal fluid specific IgG oligoclonal bands to HTLV-I were found in cerebrospinal fluid and not in serum. These laboratory findings indicated that HTLV-I could be neuropathogenic and for the first time a single etiological agent was identified in patients from different countries. Thus, in less than a decade a century of research and speculation was seemingly resolved when this disease, which was thought to occur only in blacks of poor socieconomic status in tropical countries, was shown to occur in all ethnic groups of varying socioeconomic status in temperate, subtropical, and tropical climates.

Index Entries: Tropical spastic paraparesis; HTLV-I-associated myelopathy; antibodies; retrovirus infection; inflammation.

Introduction

The search for the etiology of tropical spastic paraparesis (TSP) was fraught with frustration for many decades and the role of nutrition, toxins, and bacterial, spirochetal, and viral infection was extensively explored without success *(1,2)*. In 1985 IgG antibodies to human T-cell lymphotropic virus (HTLV-I) were found in serum of patients from Martinique *(3)*, and an etiological role of HTLV-I in these disorders seemed very likely when IgG antibodies to HTLV-I were found both in serum and cerebrospinal fluid (CSF) of TSP patients from Jamaica and Colombia *(4)*. Within 6 mo a similar myelopathy, named HTLV-I-associated myelopathy (HAM), was recognized among HTLV-I-seropositive individuals in the temperate climate of southern Japan *(5)*. Thus, a single causative agent seemed to be responsible for TSP and HAM in many regions. Furthermore, these findings indicated that the disease was not confined to blacks or mixed racial groups of low socioeconomic status and poor

nutrition in the tropics, as previously believed *(6,7)*. It was then decided that since HTLV-I-positive TSP and HAM have similar clinical features and laboratory findings, the name TSP/HAM would be used *(8)* and now TSP/HAM has been diagnosed in some sixty countries and in all racial and socioeconomic groups.

HTLV-I is now recognized to be the etiogical agent of tropical spastic paraparesis/ HTLV-I associated myelopathy (TSP/HAM), but the pathogenesis remains uncertain.

Human T-Cell Lymphotropic Virus

The most significant event in human retrovirology occurred in 1980 when human T-cell lymphotropic virus, an oncornavirus, was discovered to be the first retrovirus known to cause human disease. The disease, adult-T-cell leukemia (ATL), was first recognized in Japan and then in the United States, and significant epidemiological studies were undertaken to determine the existence of HTLV-I endemic regions.

Interest in HTLV-I waned temporarily because of the discovery of the human immune deficiency virus (HIV) as the cause of acquired immune deficiency syndrome (AIDS), but in 1985 HTLV-I regained prominence when it seemed to be the likely etiological agent of TSP. HTLV-I infection typically occurs in HTLV-I endemic regions, and the most affected are the Caribbean, South and Central America, and certain parts of Africa and Japan. The virus is transmitted via blood transfusion of infected and viable T-cells but not by plasma *(9,10)*, sexual and other intimate contact *(11)*, intrauterine or perinatal transmission via blood or neonatal transmission via breast milk *(12,13)*, and by the sharing of needles by intravenous drug abusers.

Women show a higher seroprevalence of HTLV-I infection than men and the age-related acquisition of infection that is more marked among females suggests that sexual transmission is more effective from men to women *(11)*. HTLV-I seropositivity is much higher in members of a TSP household and the mode of viral transmission among the household members is still undetermined *(14)*. Other family studies in Japan, Zaire, and Papua New Guinea show that there is a higher seropositivity for HTLV-I in families of which one or both of the parents is infected and familial occurrence of disease is well recognized *(15–17)*.

It is now quite apparent that HTLV-I infection is much more widespread than was originally thought, as reports of affected patients continue to be made from countries that had originally denied its existence, and it is now known to affect all racial groups. It is anticipated that still more evidence of HTLV-I associated disorders will continue to appear as disease awareness increases and more widespread systematic epidemiological studies are done *(18)*.

Histopathology

The histopathological features of HTLV-I infection are those of an inflammatory reaction and there is full correlation with the clinical picture. Gross examination of the brain shows no specific changes but there is often atrophy of the spinal cord. On light microscopy there are marked inflammatory changes in the spinal cord, including perivascular infiltration with lymphocytes, arterial inflammation, astrocytic proliferation, and demyelination *(19, 20)*. Electron microscopic studies show marked glial proliferation and astrocytosis *(21)*. In the more acute cases there is an inflammatory exudate around the cord and to a lesser extent the brain. The most severe inflammatory changes are seen in the thoracic region of the spinal cord, which has the poorest blood supply, and these pathological changes are more marked in the spinal cord than in brain and may also affect all organs and tissues of the body.

Pathogenesis of HTLV-I Infection: Cofactors?

Systemic infection by HTLV-I is becoming more evident as the spectrum of clinical HTLV-related disorders increases. Confirmation of this widespread organ and tissue involvement has been made by polymerase chain reaction (PCR) *(22)*. Although HTLV-I has now been identified as the primary infectious cause of TSP/HAM, it is unlikely that it is the sole etiological factor in pathogenesis. Fewer than 1% of HTLV-I-infected individuals develop ATL *(23)* and approx 2–3% may develop TSP/HAM in highly endemic areas like Tumaco in Colombia, indicating that infection with HTLV-I is not the only factor that influences disease onset. Secondary factors or cofactors appear to be necessary to initiate the disease process, whereas disease progression may be influenced by numerous environmental factors, by host-specific factors including genetic susceptibility, and by associated chronic infections that alter the host immune response.

Host genetic factors may be quite important, as evidenced by the higher frequency of disease among Blacks and Asians than among Caucasians. HLA haplotypes associated with HAM and ATL have been reported for the Japanese *(24,25)*. Similar data are not yet available for the Caribbean basin and South America, but preliminary data in Trinidad indicate that Indians have a much lower HTLV-I seropositivity than blacks, despite living in close proximity within the same environment *(26)*. A report from Ethiopia also remarks on the low prevalence of HTLV-I serpositivity in their patients with endemic spastic paraparesis (TSP) *(27)*.

Some chronic infections are frequently associated with TSP/HAM, and it is uncertain whether these infections suppress the immune system and lead to increased viral infectivity or whether the opposite occurs and these chronic infections are present because of the immunosuppression caused by HTLV-I. Their role in predisposing to disease is therefore uncertain. *Strongyloides stercoralis* infection is frequently seen in HTLV-I-positive inhabitants of Japan *(28)*, Jamaica *(29)*, and Colombia *(30)*.

Clinical Features of Tropical Spastic Parpaparesis/ HTLV-I Associated Myelopathy

In HTLV-I endemic regions TSP/HAM is the most frequently seen form of chronic spastic paraparesis and patients in all geographic regions have similar neurological and histopathological features *(7,8,31)*. The disease typically occurs in adults with onset between 30–55 yr of age but it can occur much later and earlier in life. TSP/HAM can occur in children and is also familial *(16,17)*.

A long period of latency, typically ten or more years, is found between HTLV-I infection and onset of disease *(11,32)*, however, this can be as short as 6–24 mo when disease develops following blood transfusion *(9)*. In the larger reported series there is a nearly 3:1 female to male ratio, which contrasts with some earlier studies in which the sex ratio was equal *(32,77)*. It has now been reported from Brazil that TSP/HAM patients have a younger age of onset, an equal sex incidence, and that the majority of patients are white *(33)*. These regional variations are interesting and need to be explored.

Onset of symptoms and disability may be sudden over a period of 2–7 d, but typically there is gradual onset of weakness of the legs, back pain, paresthesia, and some impairment of urinary and/or bowel function. Lack of libido and impotence also occur frequently. The main disability is spasticity and weakness of the legs that impairs motor function; vibratory sense is often impaired in the lower limbs and less frequently seen signs are impairment of postural sensibility, light touch, pinprick, and cerebellar function.

Clinically detectable dementia has been surprisingly rare and there are only three such reports to date in the world literature. Several patients may have some form of skin lesion such as ichthyosis, and a newly recognized association is infective dermatitis *(34)*. Significant lymphadenopathy was not initially recognized, but a recent study has shown the presence of persistent lymphadenopathy in infants of seropositive mothers *(13)*. A variety of systemic disorders may be associated with HTLV-I infection and some of these are seen in TSP/HAM patients *(35)*.

TSP/HAM is not usually relentlessly progressive; the course of the disease often arrests after initial deterioration and many patients have a normal life span, but others may rapidly deteriorate because of intercurrent infections and in these death is usually caused by urinary infection or pulmonary embolism *(36)*.

Treatment of patients is largely supportive since no very significant improvement has resulted from corticosteroids, plasmapheresis, or azidothymidine. The anabolic steroid danazole shows some effect on urinary symptoms although there is little or no effect on motor power or spasticity *(37)*. Both alpha and beta interferon have been used with some success in recent trials from Japan.

Clinical Spectrum of HTLV-I Disorders

Several disorders are associated with HTLV-I infection; some of these are seen in patients with TSP/HAM and others occur as a separate entity. Among these are peripheral neuropathy *(38)*, monoclonal gammopathy, sicca syndrome, cryoglobulinemia, necrotizing vasculitis, polymyositis, inclusion myositis, recurrent conjunctivitis, uveitis, lymphocytic alveolitis, amyotrophic lateral sclerosis syndrome, diabetes, sarcoidosis, hepatitis, Vogt-Koyanagi-Harada disease, ATL, chronic inflammatory arthropathy (HAP), and meningitis. The clinical spectrum continues to expand and includes isolated cranial nerve palsies, Hashimito's thyroiditis, lymphadenopathy, and infective dermatitis and pseudohypoparathyroidism. Persistent lymphadenopathy in infants of seropositive mothers and infective dermatitis were first reported from Jamaica *(13,34)*.

HTLV-I as the Only Etiological Agent of TSP/HAM

Laboratory evidence linking HTLV-I to TSP/HAM is convincing. Specific IgG antibodies to HTLV-I are found in CSF and serum in patients from different geographic areas, and multiple strains of HTLV-I have been isolated from mononuclear cells obtained from blood and CSF of patients from several countries with TSP/HAM *(17,36,39)*. HTLV-I specific IgG oligoclonal bands have been detected in CSF and not in serum *(40)*. By thin-section electron microscopy, viral particles indistinguishable from HTLV-I have been detected in the spinal cord of a Jamaican patient with TSP *(21)*, but this finding is yet to be confirmed by others. HTLV-I *gag*-encoded protein p19 has been demonstrated in spinal cord lesions of TSP patients by immunocytochemical staining *(41)* and using the polymerase chain reaction proviral DNA has been shown in the spinal cord and brain of a Caucasian TSP/HAM patient *(22)*.

A frequently associated finding in these patients is the presence of leukemia-like cells in the peripheral blood and sometimes in the CSF of TSP/HAM patients, and it is suggested that these lobulated lymphocytes are infected with HTLV-I *(5,42,43)*.

Discussion

HTLV-I is the etiological agent of TSP/HAM, but the pathogenesis remains unknown. HTLV-I is immunosuppressive but it is still unclear whether there is a direct cytotoxic effect of the virus on cells or whether there is a secondary or autoimmune process. Immunological studies indicate that there are high levels of HTLV-I cytotoxic T lymphocytes (CTL) in blood and CSF, and these could invade the central nervous system and cause demyelination. It has also been suggested that the diffusion of cytokines from these lymphocytes to a myelinated fiber could cause demyelination.

A recent laboratory study has shown that there is increased adherence of infected T-cells to endothelial cells and it has been suggested that in the initial stages of disease this is one mechanism that facilitates lymphocyte migration from the blood to the central nervous system *(44)*. The theory of genetic predisposition to disease is also not clearly understood. In Japan, specific HLA haplotypes found in HAM/TSP patients differed from that in ATL patients but the results are not conclusive and similar studies are not yet available from the Caribbean and South America. However, genetic factors could not be the single cofactor for disease development, since TSP/HAM and ATL can occur in the same patient; furthermore, the development of TSP/HAM in an identical twin and not in his or her seropositive sibling also raises questions about genetic factors *(45)*.

It is still not known if HTLV-I can be classified as a neurotropic virus, but preliminary transmission of viral isolates from TSP/HAM patients to rabbits suggests that some neurological deficit may develop. *In situ* hybridization studies have not been positive for HTLV-I RNA expression in CNS cells, although there has been expression in peripheral blood mononuclear cells in patients and carriers *(46)*.

Thus, we have many questions to be answered; however, the identification of the neuronal cells that are definitively infected would be one step toward the identification of possible source for disease development in the central nervous system. The seeming resistance of brain cells to infection is also intriguing, and similarly we must determine what factors cause the virus to be so selective in producing a single manifestation of HTLV-I infection in a given patient, since it is very rare to have two major infections in the same patient.

It is still impossible to say that prototype HTLV-I is the sole etiological agent of TSP/HAM since other strains have been implicated in disease causation. In Melanesia highly divergent sequence variants of HTLV-I have been discovered *(47)*. Efforts to seek new viruses, identify new strains, and clarify the immunological implications of this viral infection certainly provides a fertile source for future research.

References

1. Cruickshank E. K. (1956)*West Ind. Med. J.* **5,** 147.
2. Rodgers P. E. B. (1965) *West Ind. Med. J.* **14,** 36.
3. Gessain A., Barin F., Vernant J. C., Gout O., Calender A., and De-The G. (1985) *Lancet* **ii,** 407.
4. Rodgers-Johnson P., Gajdusek D. C., Morgan O. St C., Zaninovic V., Sarin P. S., and Graham D. S. (1985) *Lancet* **ii,** 1247.
5. Osame M., Usuku K., Izumo S., Ijichi N., Amitani H., Igata A., Matsumoto M., and Tara M. (1986) *Lancet* **i,** 1031.
6. Roman G. C., Spencer P. S., and Schoenberg B. S. (1985) *Neurology* **35,** 1158.
7. Rodgers-Johnson P., Garruto R. M., and Gajdusek D. C. (1988) *Trends Neurosci.* **11,** 526.
8. Roman, G. C. and Osame M. (1988) *Lancet* **i,** 651.
9. Okochi K. and Sato H. (1989) in *HTLV-1 and the Nervous System* (Roman G. C., Vernant J. C., and Osame M., eds.), Liss, New York, pp. 527–532.

10. Osame M., Izumo S., Ijichi N., Igata A., Matsumoto M., Matsumoto T., Sonoda S., Tara M., and Shibata Y. (1986) *Lancet* **ii,** 104.
11. Blattner W. A. (1989) in *Retroviruses* (Evans A. S., ed.), Plenum, New York, pp. 545–592.
12. Osame M., Igata A., Usuku K., Rosales R. L., and Matsumoto M. (1987) *Lancet* **i,** 106.
13. Pate E., Wiktor E., Murphy E., Champagnie E., Ramlal A., and Blattner W. (1989) *West Ind. Med. J.* **38 (Suppl.),** 34.
14. Arango C., Concha M., Zaninovic V., Corral R., Biojo R., Borrero I., Rodgers-Johnson P., Mora C., Garruto R. M., Gibbs, C. J. Jr., and Gajdusek D. C. (1988) *Ann. Neurol.* **23 (Suppl.),** 161.
15. Kajiyama W., Kashiwagi S., Ikematsu H., Hayashi J., Nomura H., and Okochi K. (1986) *J. Infect. Dis.* **154,** 851.
16. Kayembe K., Goubau J., Desmyter R., Vlietinck R., and Carton H. (1990) *J. Neurol. Neurosurg. Psychiatr.* **53,** 4.
17. McKhann G. II, Gibbs C. J. Jr., Mora C., Rodgers-Johnson P. E., Liberski P., Gdula W., and Zaninovic V. (1989) *J. Infect. Dis.* **160,** 371.
18. Garruto R. M., Slover M., Yanagihara R., Mora C., Asher D. M., Rodgers-Johnson P., and Gajdusek D. C. (1990) *Am. J. Hum. Biol.* **2,** 439.
19. Robertson W. B. and Cruickshank E. (1972) in *Pathology of the Nervous System,* vol. 3 (Minckler J., ed.), McGraw Hill, New York, pp. 2466–2476.
20. Piccardo P., Ceroni M., Rodgers-Johnson P., Mora C., Asher D. M., Char G., Gibbs C. J. Jr., and Gajdusek D. C. (1988) *Ann. Neurol.* **23 (Suppl.),** S156.
21. Liberski P. P., Rodgers-Johnson P. E. B., Char G., Piccardo P., Gibbs C. J. Jr., and Gajdusek D. C. (1988) *Ann. Neurol.* **23 (Suppl.),** 185.
22. Iannone R., Sherman M. P., Rodgers-Johnson P. E., Beilke M., Mora C. A., Amin R. M., Tinsley S. R., Papsidero L. D., Poiesz B. J., and Gibbs C. J. Jr. (1992) *J. Acquir. Immune Defic. Syndr.* **5 (8),** 810.
23. Ito Y. (1985) *Curr. Top. Microbiol. Immunol.* **115,** 99.
24. Usuku K., Sonoda S., Osame M., Yashiki S., Takahashi K., Matsumoto M., Sawada T., Tsuji K.,Tara M., and Igata A. (1988) *Ann. Neurol.* **23 (Suppl.),** S143.
25. Sonoda S., Yashiki S., Usuku K., Nobutaka E., Ijichi S., and Osame M. (1989) in *HTLV-1 and the Nervous System* (Roman G. C., Vernant J. C., and Osame M., eds.), Liss, New York, pp. 297–304.
26. Bartholomew C., Charles W., Saxinger C., Blattner W., Robert-Guroff M., Raju C., Ratan P., Ince W., Quamina D., Basdeo-Maharaj K., and Gallo R. C. (1985) *Br. Med. J.* **290,** 1243.
27. Abebe M., Haimanot R. T., Gustaffson A., Forsgren L., and Denis F. (1991) *Trans. R. Soc. Trop. Med. Hyg.* **85,** 109.
28. Nakada K., Kohakura K., Komoda H., and Hinuma Y. (1984) *Lancet* **i,** 663.
29. Terry S., Blattner W., Neva F., Murphy C., Murphy E. L., Golden M., Bundy D., Hanchard B., Robinson R., and Morgan O. (1989) *West Ind. Med. J.* **38 (Suppl. I),** 36.
30. Zaninovic V., Arango C., Biojo R., Mora C., Rodgers-Johnson P., Concha M., Corra R., Barreto P., Borrero I., Garruto R. M., Gibbs C. J. Jr., and Gajdusek D. C. (1988) *Ann. Neurol.* **23 (Suppl.),** 127.
31. Vernant C., Maurs L., Gessain A., Barin F., Gout O., Delaporte J. M., Sanhadji K., Buisson G., and De-The G. (1987) *Ann. Neurol.* **21,** 123.
32. Cruickshank J. K., Rudge P., Dalgleish A. G., Newton M., McLean B. N., Barnard R. O., Kendall B. E., and Miller D. H. (1989) *Brain* **112,** 1057.
33. Araujo A. de Q.-C., Afonso C. R., Schor D., Leite A. C., and de Andrada-Serpa M. J. (1993) *Acta Neurol. Scand.* **88,** 59.
34. LaGrenade L., Fletcher V., and Carberry C. (1992) *West Ind. Med. J.* **41 (Suppl. 1),** 33.
35. Jacobsen S., Zaninovic V., Mora M., Rodgers-Johnson P., Sheremata W. A., Gibbs C. J. Jr., Gajdusek D. C., and McFarlin D. E. (1988) *Ann. Neurol.* **23 (Suppl.),** S196.
36. Rodgers-Johnson P., Morgan O. St. C., Mora C., Sarin P., Ceroni M., Piccardo P., Garruto R. M., Gibbs C. J. Jr., and Gajdusek D. C. (1988) *Ann. Neurol.* **23 (Suppl.),** S121.
37. Harrington W. J., Sheremata W. A., Snodgrass S. R., Emerson S., Phillips S., and Berger J. R. (1991) *AIDS Res. Human Retroviruses* **7 (12),** 1031.
38. Bhigjee A. I., Bill P. L., Wiley C. A., Windsor I. M., Matthias D. A., Amenomori T., Wachsman W., and Moorhouse D. (1993) *Muscle Nerve (United States)* **16 (1),** 21.
39. Sarin P. S., Rodgers-Johnson P., Sun D. K., Thornton A. H., Morgan O. St. C., Gibb W. N., Mora C., McKhann G. II, Gajdusek D. C., and Gibbs C. J. Jr. (1989) *Proc. Natl. Acad. Sci. USA* **86,** 2021.
40. Ceroni M., Piccardo P., Rodgers-Johnson P. E. B., Mora C., Asher D. M., Gajdusek D. C., and Gibbs C. J. Jr (1988) *Ann. Neurol.* **23 (Suppl.),** 188.
41. Wayne Moore G. R., Traugott U., Scheinberg L. C., and Raine C. S. (1989) *Ann. Neurol.* **26,** 523–530.
42. Morgan O. St. C., Rodgers-Johnson P. E. B., Gibbs W. N., Garruto R. M., Gajdusek D. C., and Resnick L. (1987) *Lancet* **ii,** 403.
43. Johnson R. T., Griffin D. E, Arregui A., Mora C., Gibbs C. J., Cuba J. M., Trelles L., and Vaisberg A. (1988) *Ann. Neurol.* **23 (Suppl.),** S151.
44. Ichinose K., Nakamura T., Kawakami A., Eguvhi K., Nagasato K., Shibayama K., Tsujihata M., and Nagataki S. (1992) *Arch Neurol.* **49 (1),** 74.
45. Gessain A. and Gout O. (1992) *Ann. Int. Med. (United States)* **117,** 933.
46. Beilke M. A., Gravell M., Hamilton R. S., Mora C. A., Leon-Monzon M., Rodgers-Johnson P. E., Gajdusek D. C., Gibbs C. J. Jr., and Zaninovic V. (1991) *J. Med. Virol.* **33 (1),** 64.
47. Yanagihara R. (1992) *Human Biol. (United States)* **64 (6),** 843.