HTLV: TRUTHS AND QUESTIONS
REAPPRAISAL OF HTLV-I
ASSOCIATED DISEASES
(SUMMARY)

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Introduction

In 1969 the term tropical spastic paraparesis (TSP) was introduced by KS Mani, AJ Mani & RD Montgomery. These authors discussed the strong possibility that an slow virus was involved in this perplexing disorder found in India and Jamaica. Most cases used to come from predominantly rural areas, which raised the possibility of a viral reservoir in mammals or fowl. In 1986 we considered that frequent micro transfusions from hematophagous insects in the HTLV-endemic south Pacific coast of Colombia could explain at least in part the high prevalence of TSP. I proposed the term RAM (Retroviruses Associated Myeloneuropathies) for Tropical, (TSP), and non tropical, HTLV-I associated Spastic Paraparesis. Martinique, Jamaica, the south Pacific coast of Colombia, Trinidad Tobago, Dominican Republic, Seychelles, Brazil and Zaire are the most endemic regions of HTLV-I seropositive TSP. Using polymerase chain reaction (PCR), most TSP cases from south India and from Bombay were found HTLV-I seronegatives.

Since 1988 the majority of TSP cases around the world have been shown to be HTLV-I seronegative1. Kagoshima (south Japan) appears to be the unique exception with 213 similar cases, all of them (100%) HTLV-I seropositives. Curiously, in Fukuoka (south Japan), a few hundred miles from Kagoshima, in the same HTLV-I endemic Island of Kyushu, with similar HTLV-I seroprevalence and equal genetic background, only 50% of idiopathic spastic spinal paraparesis cases were HTLV-I seropositives. Theses cases were named HAM (HTLV-I Associated Myelopathy).

1. Chapter "Is it tropical spastic paraparesis due to HTLV-I only?" Zaninovic'. V. pp. 203-211.

Hypothesis
Tropical spastic paraparesis (TSP) or HTLV-I associated myelopathy (HAM), and Adult T Cell Leukemia/Lymphoma (ATLL) may be caused by Murine-Leukemia viruses (MuLVs), its variants or evolutionary mutations, in association or not with HTLV-I.

- The natural reservoir of MuLV is infected rat and wild mice.
- MuLV would be transmitted to humans by saliva, urine or feces of infected rats or wild mice.

*If this hypothesis is correct:

1. HTLV-I would be necessary but no sufficient to produce TSP/HAM, ATLL or most syndromes so far associated to HTLV-I.
2. Some existing molecular mimetism among MuLV and HTLV-I, mainly with antibodies against viral envelop, could have caused some laboratory misinterpretations.
3. False positivities to HTLV-I given by malaria, tuberculosis, leprosy and influenza may have induced statistical mistakes.
4. TSP/HAM cases associated with HTLV-II would be co-infected with MuLV or with other viruses.
5. The post transfusion case of TSP/HAM in France would be secondary to the undiagnosed MuLV infection from one of the 59 blood donors utilized in the patient during the cardiac transplantation. Of course, one or several of the blood donors was infected with HTLV-I.
6. The experimental animal model of HAM/TSP developed by Ishiguro, Yoshiki et al. in Sapporo (northern Japan) would be co-infected with some variant of MuLV.

**Epidemiological possibilities**

a) Most TSP patients are black people of low socioeconomic class living in rural areas of tropical underdeveloped countries exposed to rats, insects and parasites.

b) Southern Japanese have been also poorer and less developed than central and northern Japanese. The HAM endemic areas in south Japan are humid and semitropical with a large population of wild mice due to the production and storage of human foods.

c) Ports favor the presence of rats, mice and retroviral dissemination all over the world.

- Plantations and storage places of sugar cane, rice, corn, wheat, barley and oil palm are the natural habitats of rats and wild mice. TSP/HAM is more frequent in regions where these foods are produced, handled or stored. Woods storage and industry also favors the presence of wild mice and rats. TSP/HAM has been found in timber-merchants and lumberjacks.

e) In Mexico as well as in Cuba there are TSP cases but most of them are HTLV-I seronegative because HTLV-I seroprevalence is very low in these countries.

f) When cubans for example, go to Florida, they become infected with HTLV-I by sex or by transfusions. If these persons develop spastic paralyses while living in USA they are diagnosed as TSP/HAM. The same happens to immigrants from the Caribbean to New York and to Europe, specially to UK and France. These persons could be infected with MuLV before, or become infected after the infection with HTLV-I: If they are found later
on with HTLV-I seronegative spastic paraparesis, they are diagnosed as multiple sclerosis or as myelopathies of unknown cause as it happens in Japan.

g) More adult women develop TSP/HAM because women usually handle foods contaminated with MuLV (feces, urine, saliva). Women also are in a closer contact with wild mice and with rats either in their kitchens or in the rural areas where they work.

h) Few children develop TSP/HAM because their short age makes much less probable to be coinfected with two different retroviruses, HTLV-I and MuLV during the few years they have lived.

i) There is evidence of interspecies (non human to human) transmission of retroviruses.

The high prevalence of TSP/HAM observed in such geographic foci such as Tumaco (Colombia), Mahé in the Seychelles Islands, Lisala, and Inongo in Zaire, may reflect the high levels of HTLV-I seroprevalence, but also the presence of environmental risk factors (cofactors) yet to be determined. It is mandatory to discover those risk factors or cofactors associated with the development of HTLV-I- associated diseases; the involvement of other viruses has to be seriously considered, and on historical grounds, this is indeed probable. The mechanism of TSP/HAM pathogenesis is still hypothetical despite the large number of molecular biology and experimental data accumulated in the last few years.