HTLV-1 infection and the viral etiology of multiple sclerosis

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Abstract

The HTLV-1 virus produces a progressive inflammatory, and then degenerative, myelopathy which evolves progressively from onset. HTLV-1 is endemic in populations which are recognized as having low risk of multiple sclerosis. Multiple sclerosis generally evolves as a relapsing–remitting disease and affects predominantly Caucasians. In Caucasians, HAM/TSP can be marked by fluctuations as well as relapses. In Asians MS affects preferentially the spinal cord. The author hypothesizes that population selection through environmental factors has pushed the immune response of Caucasians towards generating relapsing–remitting disease and that of Primordial populations towards progressive disease. HTLV-1 endemity being the marker of Primordial populations and its absence that of Caucasians.

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1. Introduction

It is generally held as a definitive answer to the question of the etiology of multiple sclerosis (MS), and often repeated from one review to the next, that MS is due to a combination of genetically inherited factors and environmental factors. This statement, however, may be misleading. Indeed, recognized inherited factors are essentially congregated around the Human Leukocyte Antigen (HLA) loci, but this represents only 20% of the established inheritability of the disease and whole genome searches have not generated much more information [1]. Environmental factors are even less well recognized and remain only a suspicion as none of them has been clearly demonstrated. Among them, infectious agents and especially viruses have been suspected based on serological arguments, electron microscopic observation or even isolation, but none has withstood the test of time. Myxoviruses, viruses of the herpes family and even Chlamydia have been very high on the list of possible environmental factors, although the mechanism of interaction with genetic factors has never been established. The Human T-Lymphotropic Virus type 1 (HTLV1) was considered very briefly as a contender on the list of possible etiologic factors in MS; however it was dismissed as rapidly as it came. This comes as a surprise when one realizes that this virus is neurotropic and produces a chronic inflammatory myelopathy very similar to primary progressive MS (PPMS). Furthermore, HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP), the disease produced by the HTLV-1 retrovirus, goes through an inflammatory phase followed by a degenerative phase quite reminiscent of MS. Interestingly, Compston suggested that an evolutionary hypothesis could reconcile a genetic background and the inheritance of the Neuromyelitis Optica that predominates in primitive populations [2,3]. Our hypothesis would be similar but states that the disease inherited in primitive populations is HAM/TSP due to the HTLV-1 virus. In this review we will try and delineate how the pathological expression of a disease known to be secondary to a single virus, HTLV-1 can be altered by the genetic environment. If MS was the consequence of the encounter between a predisposed phenotype and a virus, how would both interact? How would we recognize it? Could the genetic background of the infected individual influence the expression of the disease (phenotype)?
2. Epidemiology of the HTLV-1 virus

HTLV-1 was the first human retrovirus to be discovered [4] and is endemic in certain areas of the world (especially SW Japan, the Caribbean Islands and parts of Africa and South America) where up to 10% or more of the population may be infected. It has recently been found to have low endemicity among Canadian West Coast Natives and it is probably much higher among Inuits of Northern Canada. Of note is the fact that none of the ethnic groups which carry the HTLV-1 virus seem to be predisposed to MS; all of them have a very low prevalence of MS [5]. The level of HTLV-1 endemicity varies among these populations and seems to be proportional to their degree of isolation from the outside world. The virus is transmitted through body fluids and thus individuals at risk include those belonging to high-risk ethnic groups, IV drug users, recipients of blood transfusions and sexual partners of individuals at risk (females are 10 times more affected than males). In ethnic groups at risk it appears that the virus is essentially transmitted vertically from mother to child through breast feeding. Amazingly, recipients of blood transfusion tend to develop HAM/TSP while recipients of vertical transmission tend to develop ATL.

3. Diseases linked to HTLV-1

HTLV-1 produces Acute T-cell Leukemia/Lymphoma (ATL)-making it the first human oncogenic virus- and HAM/TSP. The latter is specifically relevant to our topic because, clinically, it can closely simulate PPMS. Dermatitis, polymyositis, interstitial pneumonitis and uveitis can also be associated with HTLV-1 infection. It is also important to stress that HTLV-1 carriers can present with auto-immune disorders such as Graves disease, inflammatory thyroiditis, Sjögren disease, and diabetes mellitus type I. Candidates for association would also include the antiphospholipid syndrome, rheumatoid arthritis and inflammatory bowel disease.

4. Relation between virus and its host

It is generally accepted that carriers have less than 1 chance in 1000 to develop ATL and less than 1 in 400 to develop HAM/TSP. These numbers should be mitigated by a report from Achiron et al. indicating that over 50% of Jewish elderly repatriated from a long term care facility in Mashad (Iran) exhibited signs of myelopathy [6]. This probably underlines the fact that many of the carriers, who live in the 3rd world, probably die early of other diseases and only a few reach a ripe old age. This low lethality probably permits the virus to establish itself in the infected population. If one considers the chances for a virus to establish itself as a chronic infection in the host species, HTLV-1 is at a remarkable advantage compared to HIV, Ebola or other simian derived viruses that may produce auto-immune disorders, but may also reinforce the host capacity to defend the organism by stimulating immune reactions. Further evidence of the extraordinary adaptability of these retroviruses is the fact that a non-negligible fraction of the human genome is represented by endogenous retroviral sequences which have most probably been integrated in the ancestors’ genome eons ago. Some of these Human Endogenous Retroviruses (HERV) have been isolated more often from MS patients than from controls [7].

5. Illustrative cases

5.1. Case 1: Typical HAM/TSP in a Canadian West Coast Native

Born in 1956 this Native man from the British Columbia West Coast began having neurological problems at the age of 41. He was seen at the age of 43 with progressive spasticity in both lower extremities, urgency of urination, and a minor motor deficit in the lower extremities quoted at 5-(MRC scale), accompanied with spasticity; there was reduced vibration at the toes bilaterally, and reduced pinprick perception to mid-calf. He was walking with 2 canes. There was a post-void residue of 600 ml. Blood work showed a positive Sjögren SSA antibody at 152 (normal < 20 eu). Anticardiolipin antibodies were slightly increased at 24 units (normal < 15), brain MRI was normal, and the spinal cord MRI showed no atrophy. CSF was normal for cells, proteins and the IgG fraction was 11% (normal < 14%). Oligoclonal bands were present. HTLV-1 serology was positive. Quantitative PCR revealed a viral load of 2665 HTLV-l copies per 0.1 µg of DNA. Despite treatment with IV methylprednisolone on a monthly basis, Interferon Beta1a 30 µg IM once a week and Retrovir 400 mg/day his condition continued to worsen and at age 50 he became wheelchair bound.

5.1.1. Comments

This is the very typical presentation of HAM/TSP and most patients will fit this description: progressive inflammatory spastic paraparesis with chronic urinary retention and minor sensory symptoms. The differential from PPMS is very difficult. The fact that the patient belongs to a group in which HTLV-1 is endemic makes him highly suspect to be HAM/TSP. The oligoclonal bands in the CSF in the presence of a progressive myelopathy could have brought the suspicion of MS; however, the MRI failed to confirm HAM/TSP (early swelling of spinal cord followed by atrophy—rather reminiscent of “transverse” myelitis), nor did it show typical MS features in brain or spinal cord [8]. The serology was ordered and was confirmatory, there was no need for a diagnostic PCR.

Where is the limit of this typical phenotype of HAM? Mononeuritis, polymyositis, and Bell’s palsies have been described in HTLV-1 carriers [9]. It is very difficult in an
area of endemic disease to determine if the phenotypes are multiple or if a positive HTLV-1 serology, together with a Bell’s palsy, a root syndrome, a peripheral neuropathy or a polymyositis are co- incidental rather than representing another phenotype of the infection. Still it is conceptually possible that in a manner similar to herpes virus-induced Bell’s palsy– another phenotype of herpes virus infection in humans– there could be an HTLV-1-induced Bell’s palsy, or a peripheral neuropathy in HTLV-1 carriers. Indeed, it is difficult to evaluate if a given neurological disorder occurring in people belonging to the at-risk groups is due to the virus or not. Only when those disorders are found associated to the rare infected individuals not belonging to the at-risk ethnic group that will become convincing, unless a specific biological marker is found.

The converse is also possible: Once one has recognized the typical phenotype– severe spastic paraparesis with chronic retentive bladder and minor sensory symptoms– is it possible that, because the patient belongs to an ethnic group at risk, the retroviral etiology is suspected?

5.2. Case 2: Typical spastic paraparesis in an HTLV-1-negative Canadian West Coast Native

This West Coast Native man was born in 1942 and had progressive spastic paraparesis since age 47. This was accompanied by chronic back pain, neuritic pain in the legs and lateral thighs. There was a history of panhypopituitarism as well as type 1 diabetes. On examination he had scissoring gait, increased tone in the lower extremities with increased deep tendon reflexes, up-going toes and a large chronically retentive bladder. The MRI of the cord was normal without atrophy. MRI of the head showed a number of small focal areas of deep white matter T2 signal alterations in both hemispheres not fulfilling Barkhoff’s criteria for the diagnosis of MS. The CSF had increased cells (43/mm3) with increased IgG synthesis. CSF electrophoresis showed 2 bands in the IgG region. Antibodies to HTLV-1 were negative and PCR did not rescue HTLV-1. At last follow-up, at age 54 the disease was progressive and the patient was wheelchair bound.

5.2.1. Comments

This clinical picture is so similar to the previous one that it is difficult to not state that this is TSP. There is no family history of lateral sclerosis. There is inflammation in the CSF; therefore, could this be PPMS? The absence of serological proof or positive PCR prevents the diagnosis of HAM in this patient but the fact that he belongs to an ethnic group at risk for HTLV-1 infection increases enormously the likelihood that this is indeed HAM/TSP, possibly due to a defective virus.

Few authors have reported PCR and sero-negative clinical cases. Obviously, when the clinical presentation is typical and the cases arise in a minority at risk, the concept can be entertained that a defective virus or another very similar retrovirus, as yet unrecognized, could be responsible for the disease. Examples of supporters of such PCR-negative TSP include the group in Chile [10]. Yet, other authors think that the seropositivity can be delayed and that recent infections may remain seronegative for some time [11]. However, if such case were to occur in Caucasians would they not be diagnosed as PPMS or other inflammatory myelopathies and HAM/TSP not even suspected?

5.3. Case 3: Post-transfusion spastic paraparesis in a Caucasian man

This Caucasian man was born in 1943 and following a traumatism at age 56 he received high volume transfusion. One year later he started to complain of neuritic pseudo-radicular pains in his back and developed a very spastic paraparesis in a matter of a few days. This was accompanied by chronic urinary retention. On examination there was a sensory level at T7, weakness in both legs with increased tone, clonus bilaterally and up going toes. He also had decreased proprioception to the ankles. MRI of the head and spinal cord were normal. CSF revealed increased proteins, 14 lymphocytes/mm3 and positive oligoclonal bands. HTLV-1 serology was positive and PCR revealed 2960 copies per 0.1 μg of DNA. Since then and despite treatment he has progressed to total paraplegia and he died at age 64.

5.3.1. Comments

Except for the fact that the onset was relatively acute, this case is typical of HAM/TSP and clearly shows that the phenotypic expression of this viral illness can have typical expression on the unusual Caucasian genetic background.

This is not the case for every Caucasian and some may have relapsing remitting disease, as illustrated next.

5.4. Case 4: HTLV-1-positive spastic paraparesis in a Caucasian woman

This Caucasian woman born in 1949 was originally seen at the age of 46. She reported that at age 41 she had an acute episode of vertigo, unsteadiness and double vision, this was suspected as a brainstem attack of MS and disappeared over a few weeks. At age 43 her left leg became numb from the knee to mid thigh on the left side and this disappeared after a year or so. It may have been meralgia paresthesica. At age 45 she had Lhermitte’s phenomenon which was temporary and followed by some numbness at the level of her trunk at T5/T6. A year later she had to start self-catherization due to chronic urinary retention. This was accompanied by weakness in the legs and spasticity which progressed. On examination at age 46, she was complaining of pseudo-radicular neuritic pain at the level of the thoracic and lumbar area. Examination revealed weakness in both legs 4+/5 (MRC scale) increased tone, u-going toes bilaterally, and vibration loss up to the ankles. She had a large retentive bladder. On suspicion that this could represent HTLV-1 myelitis it was discovered that she had been using IV drugs and sharing needles from age 18 to 24 in a West Coast Native community. CSF was positive for oligoclonal bands, HTLV-
I serology and PCR were positive. Following treatment with Ziduvirine 400 mg/day and Solumedrol 1 g IV once a month she had fluctuations of her condition. At age 48, nystagmus appeared accompanied by some unsteadiness of gait that lasted only a couple of years. At age 52 she was able to walk without aid for more than 4 blocks.

5.4.1. Comment

Had the specific serodiagnosis not been ordered, the most probable diagnosis would have been Relapsing–Remitting MS. Even with a positive serodiagnosis, the question of a possible coincidence of MS and HTLV-1 infection remains. The problem would be simpler if the disease was progressive; however, here it obviously proceeded with relapses and remissions and with brainstem signs and symptoms. A non-negligible proportion of patients with HAM/TSP can have MRI abnormalities which can look very similar to MS [12]. Furthermore, among the few Caucasians which this author has followed she was the only one with a relapsing and remitting course, even though many Caucasian patients had fluctuations of their downhill course and some had a couple of relapses added to a pattern of progressive degenerative-like disease. Could this Caucasian woman have MS and be a simple carrier of HTLV-1? Or can the genotype of the patient influence the phenotypic expression of HAM/TSP?

Parallel questions can be put forward in the Japanese context where interpretation of the pattern of demyelination may have changed over time. Old MS literature from Japan clearly stressed the existence of a “Japanese-type” MS, essentially affecting the spinal cord progressively while the phenotype of relapsing–remitting MS (Western MS) was rare. Following the identification of HAM/TSP in Japan and its diagnosis split from PPMS, the “Japanese phenotype of MS” went from progressive spinal cord disease (with or without optic neuritis) to a more Western-type description; Kira et al. have attributed this to the Westernization of the way of life in Japan [13]. An alternate explanation would be that now that HAM/TSP is well identified, the small number of patients with the genetic background necessary to develop RR disease can be recognized.

How to demonstrate that the neurological disease is due to the virus in any given individual? This has been a hotly debated problem. On the one hand, the rules of neuroimmunology require that if the disease (here chronic myelopathy) is to be attributed to the virus one should be able to demonstrate intrathecal secretion of the appropriate antibody; on the other hand, virologists think that HAM/TSP occurs only in patients reaching high particle counts in their lymphocytes. The local production of antibodies can be identified on the fact that the amount of anti-virus specific IgG found in the CSF is higher than what would be expected on simple transudation. This transudation is based on the ratio of albumin levels between CSF and serum. However, a high viral load in the peripheral blood lymphocytes appears to be also a reliable marker that the disease is indeed attributable to HTLV-1 [14]. This has been included in diagnostic criteria proposed in 2006 [15].

6. Endogenous retroviruses

When a specific endogenous retrovirus was isolated from MS patients, investigators labeled it HRES (Human retrovirus endogenous element) and then MERV (MS endogenous retrovirus) [16]. Unfortunately, this evolved into evidence that these endogenous retroviral sequences could be isolated from both patients and controls and their isolation seems to be facilitated by the presence of autoimmune disorders. These findings motivated Canadian investigators to test the hypothesis that MS was linked to HTLV-1. Not surprisingly, using serology and PCR amplification they were unable to show a relationship between the diagnosis of MS and the presence of HTLV-1 markers [17,18]. This was done in Caucasian RRMS and antedated the discovery that Canadian West-Coast natives had a low level of endemicity for the virus. Indeed at that time a search of the database of the UBC MS Clinic permitted to identify 5 British Columbia Natives diagnosed as having Primary Progressive MS. On further testing they were found to be HTLV-1 positive both by serology and PCR [19]. Obviously if, by chance, these individuals had been included in the test, the outcome of this research would have been different.

7. Conclusion/hypothesis

This author does not think that one or more retroviruses represent the single etiology of MS. An alternative way of thinking would be that, as the genetic background is of primary importance in determining the disease both because MS in most ethnic groups is accompanied by an increase in the DR2 phenotype and because in this region of the genome both susceptibility and resistance genes may be expressed, it would be possible that different viruses could unlock the demyelinating process. Some patients would have a retrovirus-induced demyelination, others a Chlamidia-induced demyelination and other herpesvirus-induced demyelination, etc... With the appropriate genetic background, one would develop a relapsing disease or a progressive disease, depending on the specific genetic/ethnic background. Two types of individuals could have arisen from different selective pressures: the Northern European individual type built to generate RR disease probably selected through exanthematous viral illnesses and the Primordial type living in isolated habitats and thus preserved from epidemics but with reduced exogamic possibilities selecting an individual genetically programmed to have primary progressive disease.

References
