CASE REPORT

A Peruvian family with a high burden of HTLV-1-associated myelopathy/tropical spastic paraparesis

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SUMMARY

Human T-lymphotropic virus 1 (HTLV-1) is frequent in Peru; an estimated 1–2% of the Peruvian population carry this retrovirus. HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a chronic disabling disease that affects about 1% of the carriers of HTLV-1. It is not yet known why some HTLV-1-infected people develop HAM/TSP while others do not. In this case report, we present a family with an unusually high burden of HAM/TSP: 5 (the 2 parents and 3 of their children) of 7 HTLV-1 carriers developed the same disease. We describe the clinical presentation and discuss the clustering of disease against the current knowledge of the pathogenesis of HAM/TSP. Families such as this may hold the key to discovering which factors trigger the development of HAM/TSP.

BACKGROUND

Human T-lymphotropic virus 1 (HTLV-1) is a retrovirus that causes a lifelong infection in humans. It can be transmitted via exchange of contaminated blood, sexual intercourse and from mother to child, mainly through breast feeding. Risk factors for mother to child transmission include long duration of breast feeding, high maternal provirus load and presence of maternal HTLV-1-associated diseases.¹ Up to 10% of people infected with HTLV-1 develop associated diseases; the remaining 90% of HTLV-1 carriers stay asymptomatic throughout life.

HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a chronic disabling disease characterised by a slowly progressive paraparesis of the lower limbs, accompanied by bladder disturbances, constipation and sensory symptoms.² Patients with HAM/TSP may also suffer from other inflammatory disorders such as keratoconjunctivitis sicca and uveitis. The disease is more frequent in women than in men, and usually starts during adulthood.^{2–3} The estimated lifetime risk for an HTLV-1 carrier to develop HAM/TSP ranges from 0.3% to 4%.^{4–5} HAM/TSP is usually sporadic, affecting a single member of a family. Nevertheless, familial occurrence of HAM/TSP has also been reported in many HTLV-1-endemic regions.^{6–7}

Since only a minority of HTLV-1-infected people develop HAM/TSP, it is clear that HTLV-1 infection by itself is not the only cause of this disease. Several factors have been proposed to play a role in the development of HAM/TSP, including the route of HTLV-1 infection (infection during adulthood through blood transfusion or sexual intercourse), human genetic factors (certain types of human

leucocyte antigens (HLA)), viral factors (a possibly neurovirulent strain of HTLV-1), a high provirus load and high antibody titres against HTLV-1.^{8–10} Now, almost 30 years since the first recognised association between HAM/TSP and HTLV-1,¹¹ it is still unknown why some HTLV-1-infected people develop HAM/TSP while others do not.

Families in which several individuals develop HAM/TSP may hold the key to discovering which factors trigger the onset of this disease. We present a case of a Peruvian family with a high burden of HAM/TSP and discuss the characteristics of this family against a history of other case reports and consider the current thinking about the pathogenesis of HAM/TSP.

CASE PRESENTATION

The study of the family presented here started when the mother was diagnosed with HAM/TSP. The family consists of the non-consanguineous spouses and their 10 children (table 1 and figure 1). The mother, father and 5 of the 10 children are seropositive for HTLV-1 on ELISA and western blot. The remaining five children are seronegative. Before the diagnoses of HTLV-1 infection, no one in this family had received blood transfusions or had used intravenous drugs, leaving breast feeding of the children and sexual intercourse among the parents as the most likely routes of HTLV-1 transmission.

The mother, father and three of the children developed HAM/TSP; their disease evolution according to Kurtzke's expanded disability status scale (EDSS) is shown in figure 2.

Index case

In 1997, a 46-year-old woman who was born in the Andean highlands of Peru presented at the Instituto de Medicina Tropical Alexander von Humboldt (IMTAH) with a 2-year history of insidious gait problems and stumbling. The symptoms started around the time of birth of the youngest of her 10 children.

At the first physical examination in 1997, her main symptoms were weakness and a burning sensation in the lower limbs, bladder disturbances and constipation. She presented signs of upper motor neuron lesion: spasticity, brisk tendon reflexes of the lower limbs and an abnormal extensor plantar reflex (Babinski sign). She could still walk, however, she required a cane. As far as she knew, no other members of her family had gait problems or leukaemia/lymphoma, another complication of HTLV-1 infection. She was diagnosed with HTLV-1 infection and HAM/TSP. Muscle relaxants and pain

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Table 1 Demographical and clinical characteristics of the family members

Subject	HTLV-1 status*	Sex	Ethnic origin	Breast feeding, duration (years)	Year of birth	Age (year) onset of HAM/TSP	HTLV-1-associated diseases	Comorbidities	Provirus load†
Index case	Positive	W	Andean	Yes, NK	1951	44 (1995)	HAM/TSP, O	Brucellosis; tonsillitis; gallbladder stones	1475
Husband	Positive	M	Nikkei	Yes, NK	1951	60 (2011)	HAM/TSP, SS	Hernia; hypertension; coronary disease	4164
Child 1	Negative	W	Mestizo	Yes, 1	1974	NA	NA	None	NA
Child 2	Negative	M	Mestizo	Yes, 1–2	1975	NA	NA	None	NA
Child 3	Negative	W	Mestizo	No	1978	NA	NA	None	NA
Child 4	Positive	W	Mestizo	Yes, 1–2	1979	NA	Asymptomatic carrier	Gallbladder stones	986
Child 5	Positive	M	Mestizo	Yes, 1–2	1981	15 (1996)	HAM/TSP, IDH	Skin allergy, Pityriasis versicolor	4261
Child 6	Positive	W	Mestizo	Yes, 1–2	1983	14 (1997)	HAM/TSP, IDH, O	Migraine; third-degree skin burn	3965
Child 7	Positive	W	Mestizo	Yes, 1–2	1986	12 (1998)	HAM/TSP	None	1974
Child 8	Negative	M	Mestizo	Yes, 1–2	1989	NA	NA	None	NA
Child 9	Negative	W	Mestizo	Yes, 1–2	1992	NA	NA	None	NA
Child 10	Positive	W	Mestizo	Yes, 6	1995	NA	Asymptomatic carrier	Cellulitis/septic arthritis in knee; enterobiasis	129

*Diagnosis by ELISA and/or western blot.

†Number of HTLV-1 copies/10⁴ peripheral blood mononuclear cells, median when more than one measure available.

HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-lymphotropic virus 1; IDH, infective dermatitis associated with HTLV-1; M, man; NA, not applicable; NK, not known; O, onychomycosis; SS, *Strongyloides stercoralis* infection; W, woman.

killers were prescribed, but she may have taken them irregularly and the response was poor.

Fifteen years later, she could not walk and was confined to a chair or bed, but she could still use her upper limbs and was capable of performing some of her daily activities (figure 2). She had undergone multiple episodes of urinary tract infection during the course of her disease.

Husband

The husband of the index case was 47 years old at his HTLV-1 screening in 1998. The couple had been living together for 26 years. He was born in Huánuco, in the central highlands of Peru, but his grandparents came from Kumamoto, on Kyushu Island in Japan. He reported that he had been breastfed but did not know for how long.

He remained asymptomatic until 2007, when he started reporting pain and weakness in the lower limbs, and constipation. At that time, the neurological examination was still normal. He presented eosinophilia and was tested for parasites. He had a positive stool test for *Strongyloides stercoralis*, for which he received therapy and had a negative stool test at follow-up.

In 2011, after a coronary bypass surgery, he reported constant stumbling, constipation and nocturia. At that time, he presented typical signs of HAM/TSP on neurological examination: spasticity, hyper-reflexia, clonus, bilateral Babinski sign and left Hoffman sign. He was diagnosed with HAM/TSP, but he could still walk unaided and was able to perform his daily activities independently (EDSS: 4, figure 2).

HTLV-1-positive children

The 4th (C4) and the 10th (C10) child were diagnosed with HTLV-1 at ages 20 and 4 years, respectively. Currently, they are considered to be asymptomatic carriers of HTLV-1. The fifth (C5), sixth (C6) and seventh (C7) child were diagnosed with HTLV-1 and HAM/TSP. The cases of C5 and C6 are described in detail.

The *fifth child* (C5) was 18 years old when he was diagnosed with HTLV-1 infection and HAM/TSP, in 1998. His disease started when he was 15 years of age, with stumbling and weakness in the lower limbs. At the time of diagnosis, he presented the typical symptoms and signs of HAM/TSP. By the age of 23 years, he was severely disabled; he had severe spasticity, urinary incontinence, vesical tenesmus and lumbar pain. He could still walk a few metres, using a cane, but he required a wheelchair to mobilise out of the house. During further follow-up, his disease remained relatively stable (figure 2). At the age of 33 years, he presented exudative lesions on the scalp and was diagnosed with infective dermatitis. In addition, he had pityriasis versicolour on his trunk.

The *sixth child* (C6) was 16 years old when she was diagnosed with HTLV-1 and HAM/TSP. She had a history compatible with childhood infective dermatitis. The symptoms of HAM/TSP started when she was 14 years of age, with numbness in the lower limbs. By the age of 21 years, in 2004, she had severe manifestations of HAM/TSP: weakness in the lower limbs, lumbar pain, paraesthesias, burning pain, urinary incontinence, vesical tenesmus, constipation, moderate spasticity,

Figure 1 Pedigree of the family. Circle, woman; square, man; black dot, human T-lymphotropic virus 1 (HTLV-1) carrier; yellow shade, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP); arrow, index case.

Figure 2 Disease progression of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) cases according to Kurtzke's EDSS. EDSS, expanded disability status scale; I, index case; H, husband; C5, child 5; C6, child 6; C7, child 7.

myoclonus, hyper-reflexia and bilateral Babinski sign. At that time, she could still walk, however, she required the aid of a cane (EDSS: 6). She received muscle relaxants and pain medication, but had poor response. Currently, she is able to walk a few steps with a walker, but is mostly confined to a wheelchair (figure 2).

DISCUSSION

We present a family with a high burden of HAM/TSP. Given that the lifetime risk for an HTLV-1 carrier to develop HAM/TSP is <5% and that HAM/TSP usually has a sporadic presentation, it is striking that five of seven HTLV-1 carriers in this family developed HAM/TSP.

Familial occurrence of HAM/TSP has been reported worldwide. One of the earliest reports came from the Democratic Republic of Congo (Equateur Province). It describes a series of 10 families with more than one case of HAM/TSP per family. In seven of these families, HAM/TSP affected the mothers and some of their children and grandchildren.⁶ Another report from Tumaco, Colombia, describes one family in which the spouses and their son were affected by HAM/TSP.¹² More recently, a study in Kagoshima, Japan, found that about 5% of 784 patients registered at a referral hospital with a diagnosis of HAM/TSP had relatives with HAM/TSP, mostly parents, children or siblings.¹³

As in previous reports of familial HAM/TSP, the patients described in this report presented the typical clinical manifestations of the disease, although their children developed HAM/TSP at an unusually young age. This is in line with a report from Japan, which mentions the early onset of HAM/TSP in families with more than one HAM/TSP case. The same report from Japan also suggests that the course of familial HAM/TSP could be less severe than the course of sporadic HAM/TSP.¹³ This does not appear to be the case in this family, in which three of the five patients could not mobilise without a wheelchair.

Multiple hypotheses have been put forward to explain the pathogenesis of HAM/TSP. In theory, a neurotropic strain of HTLV-1 could explain the aggregation of HAM/TSP in this family, because the different relatives are most likely carriers of

the same virus. One study in Japan found that different *tax* subgroups may influence the risk of developing HAM/TSP.⁸ Nevertheless, several other studies failed to find a clear link between specific viral variants and the clinical outcomes of HTLV-1 infection.^{14 15}

Human genetic factors have also been proposed as a possible cause of increased vulnerability for HAM/TSP. Several studies have compared genetic characteristics of HTLV-1 carriers with and without HAM/TSP. Most of these genes encode proteins, such as HLA^{10 16} and cytokines,¹⁷ that play a role in the cellular immune response. Furthermore, it is well known that genetic mutations alone—in people without HTLV-1—can cause hereditary spastic paraparesis, a syndrome that resembles HAM/TSP. Hereditary spastic paraparesis has been linked to diverse genetic variations that result in a similar neurological syndrome.¹⁸ Whether or not there are genetic similarities between hereditary spastic paraparesis and familial HAM/TSP has not yet been assessed.

The HTLV-1 provirus load is a result of the interaction between the virus and the host immune response. High provirus loads have been linked to the presence of HAM/TSP and other HTLV-1-associated diseases.⁹ Two studies have suggested that relatives of HAM/TSP patients tend to have higher proviral loads than non-HAM/TSP relatives.^{9 19} In the family in this report, the five members with HAM/TSP presented higher provirus loads than their asymptomatic relatives.

Other explanations put forward to explain the susceptibility to HAM/TSP include horizontal transmission of HTLV-1 (ie, transmission via sexual intercourse or organ transplantation) and environmental factors. Nutritional factors that have been linked to paraparesis include vitamin B₁₂ deficiency, folate deficiency, malnourishment, toxicity due to the consumption of cyanide-containing bitter cassava, lathyrism, konzo, and oral and topic clioquinol intoxication.²⁰

The rather uniform clinical appearance of HAM/TSP tends to suggest that it is caused by one, yet unknown, pathological mechanism. Another possibility is that long central nervous system axons (such as corticospinal tract and dorsal column fibres) are particularly vulnerable to distinct disturbances. Different mechanisms could then lead to only one clinical

syndrome, as the repertoire of symptoms of the corticospinal tract is limited. This seems to be the case in hereditary spastic paraparesis, where heterogeneous genetic mutations can lead to one clinical outcome.¹⁸ This view of different possible mechanisms leading to one disease may help to assimilate information from families such as the one presented here, in which we could not think of a single mechanism explaining disease in the affected individuals.

The case presented here illustrates the devastating impact that HAM/TSP can have on the prospects of a whole family. It also demonstrates how little is known as yet about the causes and pathogenesis of HAM/TSP. Nevertheless, families such as this may hold clues as to which factors trigger the onset of HAM/TSP. These insights would bring us one step closer to real prevention or treatment.

Learning points

- ▶ Families in which several individuals develop Human T-lymphotropic virus 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) have been reported worldwide.
- ▶ Familial HAM/TSP represents a heavy burden on the family, and the clinical presentation of familial HAM/TSP (eg, earlier age of onset) may differ from that of sporadic HAM/TSP.
- ▶ In families with several cases of HAM/TSP, the disease may affect blood relatives as well as in-laws.
- ▶ A single mechanism to explain the pathogenesis of HAM/TSP has not yet been found. Instead, considering HAM/TSP as one clinical outcome that can be caused by several different mechanisms may facilitate a better understanding of this disease.
- ▶ Family aggregation studies may be a useful epidemiological tool for unravelling the pathogenesis of HAM/TSP.

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