Case Series: Pediatric Human T-Lymphotropic Virus Type 1 and Its Clinical Expression

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Purpose: Human T-lymphotropic Virus type 1 (HTLV-1) was the first retrovirus to be identified and associated with oncogenic activity. It is estimated that approximately 10–20 million people in the world are infected with it. The clinical manifestations most commonly associated with HTLV-1 infection include T-cell leukemia/lymphoma and myelopathy associated to HTLV-1 infection. The purpose of this study is to describe clinical and demographic characteristics in pediatric patients with HTLV-1 infection.

Methodology and Patients: Ambispective case series analysis, with collection of medical records and subsequent description of demographic data (sex, origin, age) and clinical characteristics in 16 patients with HTLV-1 infection were collected. Twelve of these patients were part of an initially reported cohort and four were recruited later in the study. The patients were collected between January 2017 and July 2021 in a pediatric institution in Cali, in a reference hospital in the southwest region of Colombia.

Results: Thirteen of a total of sixteen patients came from the Colombian Pacific coast, where nine were with significant nutritional deficiencies. Seven showed dermatological compromise. Eight patients presented images compatible with inflammation and chronic lung injury, and six of the eight patients were with opportunistic infections. Coinfection with other microorganisms was also observed where one case presented with meningeval tuberculosis, another patient presented with simultaneous infections, namely, malaria, leptospirosis and toxoplasmosis, and a third patient presented intestinal parasitosis and soft tissue infection by Streptococcus pyogenes. Three patients had concomitant autoimmune diseases and a fourth patient was highly suspicious of having polyomyositis.

Conclusions: The different clinical findings with simultaneous HTLV-1 infection broaden the panorama to suspect infection by this virus. More studies are required to achieve a direct association between structural lung disease, autoimmune diseases, immunodeficiency and HTLV-1 infection. This study aims to raise interest and awareness of an ancient but neglected disease.

Keywords: tropical medicine, retrovirus, Human T-cell lymphotropic virus type 1, oncogenic virus, case series
INTRODUCTION

Human T-lymphotropic virus type 1 (HTLV-1) is a retrovirus with oncogenic properties that affects around 10 to 20 million people worldwide (1). The clinical manifestations most commonly associated with HTLV-1 infection include T-cell leukemia/lymphoma (ATLL) and myelopathy associated to HTLV-1 (HAM) (2–4). Studies carried out mainly in the adult population have reported other clinical manifestations, namely, chronic inflammatory and autoimmune diseases (uveitis, polymyositis, thyroiditis and alveolitis), co-infections by opportunistic microorganisms, malnutrition, depression, and interstitial lung disease (5–7). The opportunistic microorganisms that have been associated to HTLV-1 include Mycobacterium tuberculosis, Strongyloides stercoralis, infective dermatitis associated to Staphylococcus and Streptococcus infections (8–10).

The prevalence of HTLV-1 infection in children in Colombia is still unknown, being extrapolated from studies of this virus in other population groups such as blood donors and in endemic populations of the Pacific region (11). In 1992 a study was published by Trujillo et al., in which the seroprevalence of HTLV-1 was analyzed in a group of 1,077 individuals in the city of Tumaco, reported a seroprevalence of antibodies against HTLV-1 in 2.8% in this population (12). Later a study published in 2016 by Macia et al. in blood donors from a hospital in the city of Cali, found an accumulative seroprevalence of 0.24% in their population (13). A national study conducted by the country’s blood bank network demonstrated a prevalence of HTLV-1 and 2 antibodies in nationally donated blood between 2001 and 2014 of 0.3%. This value was higher in the state of Chocó with an antibody reactivity of 6.28% of the donated units, 20 times higher than the national average. In the states of Córdoba, Cauca, Antioquia, Caldas, Casanare, and Magdalena, the prevalence was found between 1.7 and 3.1 times higher than the national average (14). It should be noted that the majority of infected people are asymptomatic or present mild symptoms (approximately 90% of the population), facilitating the different transmission mechanisms due to this carrier state (8, 11).

The mechanisms of transmission of the virus can be grouped into three main forms: vertical transmission from mother to child, unprotected sex, and contamination of blood products (8, 15). Regarding mother-to-child transmission prolonged exposure to breastfeeding is the main form of transmission (16). The literature shows that this transmission varies from 7.4 to 32%; this variation is explained by the breastfeeding time exposure (17). In Japan it is reported that a seroconversion of 15.7% occurs in breastfed infants during more than 12 months vs 3.6% in bottle-fed children (18). In Jamaica the difference was 32% in a group of infants breastfed during more than 12 months vs 9% in children breastfed for a shorter duration (17, 18). A possible explanation for this association is that maternal antibodies are received during fetal life inhibits HTLV-1, but disappears at 6 to 12 months of life generating infection to the infant in this period (19). In a study carried out on Peruvian mothers with HAM, the infection rate to their children varied depending on the time of exposure, being 4% when breastfed for less than 6 months, 15% in those breastfed between 6 and 12 months and 28% in those breastfed between 12 and 24 months (8, 20). The other important aspect in transmission is the proviral load, which represents the number of the cells infected by HTLV-1; this supports the concept that transmission is associated with infected cells and not by transmission of the free virus, which is attributed lower virulence (21).

One of the measures implemented to reduce the transmission of the virus is through control and screening of the virus in blood banks. Colombia is one of the few Latin American countries that have screening for this disease; however this mechanism of transmission is not the one that predominates in the pediatric population (13). Other measures have been used to decrease transmission through the prevention of vertical transmission. This has been achieved through prenatal screening of HTLV-1 in women. Those who are seropositive for the virus are recommended a maximum of 6 months of breastfeeding. This method has been carried out in Japan with striking results, demonstrated by the study carried out in Nagasaki, where a reduction in the prevalence of HTLV-1 went from 20.3 to 7.5% by applying this measure and a reduction of 2.5% in complete bottle-fed newborns (22). In Colombia, the diagnosis of HTLV-1 is not part of the prenatal control screen even though we are an endemic area for this disease.

HTLV-1 infection has been studied mainly in the adult population, being recognized as a causative agent of adult ATLL and HAM (23, 24). Approximately 2–7% of the people infected by HTLV-1 are at risk of developing ATLL and 0.25–3% HAM (10, 23, 25). ATLL is described as an aggressive lymphoproliferative malignancy involving T lymphocytes with a reported survival of 5%, commonly developing around the age of 20 to 30 years and associated with vertical transmission through breastfeeding (26). HAM is a chronic meningomyelitis that involves both white and gray matter in the spinal cord, producing demyelination and axonal degeneration. It is clinically expressed with progressive spastic paraparesis, bladder and intestinal dysfunction and has an average age of presentation at the age of 40 (24, 25, 27, 28).

Few studies evaluate the clinical manifestations of this disease in children, most of the findings have focused in dermatologic manifestations, being infective dermatitis the main description. LaGranade et al. described infective dermatitis in fourteen Jamaican children between the ages of 4 and 17 years, who were screened for HTLV-1 and all of them tested positive for this disease (29). More recently a report of forty-two children with HTLV-1 was followed in Bahia, Brazil (30). The age range was 2 months to 11 years, with a mean age of onset of the dermatitis 2.6 years and an age of resolution between 10 and 20 years (30). Additionally, there are 17 well documented cases of HAM in children and adolescents found in the literature, where twelve of them had the additional finding of infective dermatitis (31).

The association of HTLV-1 with chronic and autoimmune inflammatory diseases has also been described in children, in which the viral genome and/or viral proteins have been detected in the target tissue of patients with these symptoms (10, 23).
These include uveitis, arthropathy, bronchoalveolar pneumonitis, autoimmune thyroiditis, Sjögren’s syndrome and polymyositis (10, 32, 33). However, with the exception of uveitis, an epidemiological association between HTLV-1 and autoimmune diseases still requires more evidence (10).

Several opportunistic infections have also been documented in association with HTLV-1 infection, among which are: tuberculosis, pulmonary aspergillosis, cytomegalovirus pneumonitis, and strongyloidiasis hyperinfection syndrome, suggesting secondary immunodeficiency associated with this virus (8, 10). Additionally infective dermatitis has been a frequent manifestation in the pediatric population, associated with staphylococcal and streptococcal skin infections (34).

The purpose of this study is to do a follow up of a case series previously presented with the addition of a new group of patients expanding the description of the clinical and demographic characteristics in pediatric patients with HTLV-1 infection.

METHODOLOGY

Ambispective case series analysis, with collection of medical records and subsequent description of demographic data (sex, origin, age) and clinical characteristics in sixteen patients with HTLV-1 infection were collected. Twelve of these patients were part of an initially reported cohort and four were recruited later in the study. The patients were collected between January 2017 and July 2021 in a pediatric institution in Cali, in a reference hospital in the southwest region of Colombia.

RESULTS

Information was collected from sixteen patients with a confirmatory Western Blot test for HTVL-1; nine were men and seven were women. The proviral load was not available for the patients evaluated. Twelve patients were reported in the initial series, with an additional of four patients recruited for this work (35). Of a total of sixteen patients, thirteen patients came from the Colombian Pacific coast, namely, the states of Valle del Cauca, Chocó, Cauca and Nariño. The ages of presentation were variable, namely, three infants, ten school aged children and three adolescents. The nutritional status of the patients was evaluated according to the data provided in the clinical history, considering percentiles height for age in patients younger than 5 years and body mass index (BMI) for age in patients older than 5 years, finding nine of the sixteen patients with a classification of malnutrition.

Nine patients showed hematological alterations, in which the expression of microcytic normochromic anemia. Only two of the sixteen patients showed cytopenia in two blood lines in whom lymphoproliferative disease was ruled out with flow cytometry; therefore, none of the patients had clinical features suggestive of ATLL.

Among the neurological manifestations, sudden loss of visual acuity associated with headache occurred in one of the cases, without other neurological symptoms suggesting uveitis, later classified within the Vogt–Koyanagi–Harada syndrome. The second case that shows neurological manifestations is a patient with a febrile episode, associated with a seizure and subsequent right hemiparesis and nystagmus. Images including both, computed tomography (CT) and magnetic resonance (MRI) documented a cerebral ischemic stroke with meningeal enhancement of the middle cerebral artery, and changes in cerebrospinal fluid (CSF) suggested meningeal tuberculosis. The third case in which neurological manifestations were described has a chronic clinical history of loss of strength, progressive limitation that predominated in the lower limbs. MRI of the lower limbs shows muscle hypotrophy, with findings suggestive of inflammatory or dystrophic myopathy, and an electromyography with neuroconduction that shows chronic and active denervation of proximal distal muscles with poor recruitment of distal muscles. The most likely diagnosis was polymyositis vs Limb-girdle muscular dystrophy. There are no documented cases of neurological involvement or manifestations consistent with HAM.

In terms of autoimmune or chronic inflammatory disease, three patients were found with pathologies attributable to autoimmunity, and a fourth patient found in the second cohort in whom it is among the possible differential diagnoses. The first case is a 6-year-old patient with malnutrition and failure to thrive, fever, hematochezia, and long-standing intermittent diarrhea. Serial stool studies are performed, ruling out infection by opportunistic parasites, or acute bacterial diarrheal disease. A colonoscopy with intestinal biopsies confirmed the presence of inflammatory bowel disease. The second case is a patient with prolonged hospitalization with suspected sepsis and in need of treatment in the intensive care unit (ICU), with severe thrombocytopenia and hemolytic anemia. His final diagnosis is immune thrombocytopenic purpura, with previous studies that ruled out infectious causes and lymphoproliferative disease by flow cytometry. This patient additionally manifests dermatological lesions compatible with scabies. The third patient is a female patient with acute fever and general symptoms that progress to sudden bilateral amaurosis, with a final diagnosis of Vogt–Koyanagi–Harada Syndrome.

The presence of respiratory symptoms predominated in the first cohort with a subsequent finding of chronic lung disease, manifested by radiological changes corroborated by CT scans that occurred in eight of the sixteen patients. The presence of bronchiectasis is the main characteristic of lung damage and the principal image findings were subpleural cystic and areas of ground glass that predominate in apical locations. Among other findings described are pleural thickening, cavitations or bullae, fibroelastic bands and atelectasis, and lastly budding tree nodules. Of these eight patients with chronic lung disease, bronchoalveolar lavage was performed in all of them to expand studies due to the severe compromise. Through bronchoalveolar lavage possible etiology was evaluated with microorganism cultures, galactomannan studies, GeneXpert, and multiplex polymerase chain reaction (PCR) technique for bacterial or viral detection. Two of the patients showed positive PCR for M. tuberculosis, and four patients had a positive galactomannan
test (cut-off point >0.5) in bronchoalveolar lavage that was suggestive of pulmonary aspergillosis.

Aside from pulmonary infections there were other infections detected in patients infected with HTLV-1, which predominated in the second cohort group. A 1-year-old patient with intermittent fever, subsequent seizure event and right hemiparesis associated with nystagmus, mentioned previously had a final diagnosis of meningoencephalitis. He had a family history of a father with active pulmonary tuberculosis with poor adherence to treatment. The CSF cytological study was compatible with meningial tuberculosis and CT and MRI showed compromise of middle cerebral artery flow (vasculitis process) and meningoencephal enhacement, compatible in the context of the patient, with meningeal tuberculosis.

A second patient was admitted due to prolonged fever, cough, headache and general symptoms. During the initial evaluation a moderate microcytic hypochromic anemia and thrombocytopenia was evident, with later flow cytometry that ruled out lymphoproliferative disease. Within the search of the etiology of the prolonged febrile syndrome, positive IgM serology was observed; hence HTLV-1 infection was suspected and confirmed by Western Blot test.

The last patient with HTLV-1-associated coinfections was a 3-year-old patient who was admitted with evidence of infective dermatitis and a neck mass; ultrasound evidenced multiple posterior cervical and laterocervical lymphadenopathy suggesting an inflammatory and/or infectious process. The patient was taken to surgical drainage with isolation of a Streptococcus pyogenes, diagnostic of mixed malaria. Due to the coinfection of multiple microorganisms (parasites and bacteria) immunity studies were completed, ruling out infection by human immunodeficiency virus (HIV) and no compromise of immunoglobulin levels was observed; hence HTLV-1 infection was suspected and confirmed by western blot.

Skin involvement was also explored, describing five cases with lesions compatible with infective dermatitis, and two cases of scabies. Tables 1 and 2 contain a summary of the cases and characteristics described.

**DISCUSSION**

This study describes the clinical and demographic characteristics of sixteen patients diagnosed with a HTLV-1 infection confirmed by Western Blot test. As described in the literature, the pathologies that have been shown to be directly associated with HTLV-1 infection are HAM and ATLL; however these pathologies are mainly described in adults (10, 23–25). In this case series, we observed that within the neurological and hematopoietic manifestations, none were related to what was described for HAM or for ATLL, but the evolution towards any of these complications is not ruled out since the average age of presentation has been described in the third and fourth decades of life (23).

Dermatologic lesions have been frequently associated with HTLV-1 in children, specifically infective dermatitis. In the patients evaluated five of the sixteen patients had lesions compatible with infective dermatitis, and two more patients presented scabies. In the literature and up to now in pediatrics, there is the only one known to have a direct causal relationship with HTLV-1 infection (33, 34). The onset of the dermatitis occurs around 2 years of age, and comes very often associated with infections with *Staphylococcus*, *Streptococcus* and scabies as we have seen in this series, possible secondary to the dysregulation of the immune system (36).

One of the cases described in the last cohort is a patient with progressive loss of gait and progressive muscle compromise with signs of active inflammation and sequelae that are not compatible with HAM, since he doesn’t present paresis. However, the described characteristics could correspond to polymyositis, which has been described previously in the literature as one of the expressions of autoimmunity present in patients with HTLV-1 (35, 37, 38).

| Patients | Age in Years and Sex | Place of Residence | Concomitant Infections | Dermatologic Compromise | Autoimmune Compromise |
|----------|----------------------|-------------------|------------------------|------------------------|----------------------|
| CASE 1   | 14 M                 | Buenaventura, Valle del Cauca | Pulmonary aspergillosis | No                     | No                   |
| CASE 2   | 8 F                  | Mosquera, Nariño    | Pulmonary aspergillosis | No                     | No                   |
| CASE 3   | 10 F                 | Buenaventura, Valle del Cauca | Pulmonary tuberculosis | Yes, scabies           | No                   |
| CASE 4   | 8 M                  | Puerto Merizalde, Valle del Cauca | Pulmonary tuberculosis | No                     | No                   |
| CASE 5   | 16 M                 | Timbiquí, Cauca     | None                   | Yes, infective dermatitis | No                   |
| CASE 6   | 6 F                  | San Isidro, Valle del Cauca | None                   | Yes, infective dermatitis | No                   |
| CASE 7   | 6 M                  | Tumaco, Nariño      | None                   | Yes, infective dermatitis | Inflammatory bowel disease |
| CASE 8   | 7 F                  | Buenaventura, Valle del Cauca | Pulmonary Aspergillosis | Yes, infective dermatitis | No                   |
| CASE 9   | 16 M                 | Buenaventura, Valle del Cauca | Pulmonary Aspergillosis | No                     | No                   |
| CASE 10  | 1 M                  | Medio San Juan, Chocó | None                   | Yes, scabies           | Immune thrombocytopenic purpura |
| CASE 11  | 12 F                 | Cali, Valle del Cauca | None                   | No                     | Panuveitis - Vogt Kayanagi Hadara syndrome |
| CASE 12  | 1 M                  | Buenaventura, Valle del Cauca | None                   | No                     | No                   |
### TABLE 2 | Characteristics of patients infected by HTLV-1-second cohort.

| Patients | Age in Years and Sex | Place of Residence | Concomitant Infections | Dermatologic Compromise | Autoimmune Compromise |
|----------|----------------------|--------------------|------------------------|-------------------------|----------------------|
| CASE 13  | 11 F                 | Cali, Valle del Cauca (Family with residence in Chocó) | Toxoplasmosis, leptospirosis, dengue y malaria | No | No |
| CASE 14  | 1 M                  | Cali, Valle del Cauca | Meningeal tuberculosis | No | No |
| CASE 15  | 5 F                  | Pradera, Valle del Cauca | None | No | Polymyositis under study |
| CASE 16  | 3 M                  | López de Micay, Cauca | Intestinal parasitosis by Ascaris lumbricoides, Trichuris trichiura, Soft tissue infection by S. pyogenes | Yes, infective dermatitis | No |

The most frequent expressions in this group of patients were respiratory manifestations with secondary pulmonary involvement. The deficient T lymphocyte response to infection caused by invasion of the virus has been proposed as a possible pathophysiologic mechanism of inflammatory disease both at the lungs and in other systems (9, 39). In case series in the adult population of Australian aborigines and in Japanese series, the radiological images found were centrilobular nodules, ground glass opacities and bronchovascular thickening (bronchiectasis); compatible with what is found in this series (40). In addition to the damage to the lung structure, there is an overlapping infection by *M. tuberculosis* that has also been described in the literature, observed in two of the sixteen patients described (9, 23, 35). In a study carried out in Brazil, they attributed a three times greater risk of acquiring pulmonary tuberculosis when there was a HTLV-1 infection, both reflecting conditions of vulnerability and poverty in this group of patients (9). Another study in Peru evaluated the medical history of a cohort of HTLV-1 patients and their close relatives finding an increased susceptibility to tuberculosis in this group of patients (41). Within the realm of possible infection by opportunistic microorganisms, so far no association with *Aspergillus* infection has been documented in the pediatric population. However, in this series four of the sixteen patients were found with this condition. Both *Aspergillus* and *M. tuberculosis* can perpetuate lung damage and drastically deteriorate the quality of life of the patient, and even increase mortality, so an active search for these possible agents is suggested since it is treatable.

The finding of meningeal tuberculosis has been described less frequently, mainly reports of cases and case series in the adult population (42, 43). In the case described with documented meningeal tuberculosis, an inflammatory process that led to vessel damage and consequent ischemic event with neurological sequelae that occurred associated with this coinfecion.

The dysregulation in the immune response is not only reflected in immunodeficiency, but also in a response to autoantibodies, generating a direct correlation between immunosuppression and autoimmunity (44). This is why the pathophysiologic mechanism of the viral integration to T lymphocytes with consequent dysregulation in their function has been correlated with the expression of different autoimmune diseases, in which uveitis, polymyositis, arthritis, Sjögren’s syndrome, thyroiditis, etc., have been associated to this disease. In the first cohort we found 3 patients with confirmed diagnoses of autoimmune diseases, namely, posterior pan uveitis (Vogt–Koyanagi–Harada syndrome), immune thrombocytopenic purpura, and inflammatory bowel disease. One of the cases in the last cohort could correspond to polymyositis, the case is still under study.

The last two cases are associated with overlapping infections found in second cohort group. The first case is an adolescent female who despite not having opportunistic microorganisms, was found to be positive for multiple infections, leptospiira, toxoplasma and mixed malaria infection (vivax and falciparum), led to think about the possibility of some degree of alteration in the immune response. The second case is a child with characteristics of infective dermatitis but who additionally had intestinal parasitosis associated with detection of two parasites *A. lumbricoides* and *T. trichiura*, and additionally with a soft tissue infection by *S. pyogenes*. This makes HTLV-1 infection part of the range of possibilities when there is a suspicion of immunosuppression.

The presence of malnutrition was a very frequent finding in this case series, evident in nine of the sixteen patients, but it is difficult to assure an association between HTLV-1 infection and malnutrition. The social condition of the areas of origin of these patients itself confers a degree of vulnerability, nutritional deficiencies and barriers for accessing health care which contribute to this result. Although studies have described increased nutritional risk in patients hospitalized for HTLV-1 in Brazil similar to what was observed in this case series (7). Because this is a neglected infection that prevails in countries already affected by poverty and other public health problems, there has been little interest in expanding knowledge about this disease, such as studies to establish the real epidemiology, policy measures to impact its transmission, and therapeutic options to treat the disease. In addition, most of the endemic areas for HTLV-1 are typically areas of social inequality, which makes the study of the disease difficult and ads an additional burden to a population with already a heavy burden of poverty.

In case series studies, such as the current one, whose objective is only to describe and characterize patients with a certain factor in common, it is difficult to calculate the measure of risk conferred by HTLV-1 to the development of these pathologies, however the intention of the study is to broaden the range of possibilities in the diagnosis of this infection. This information can be used to provide the patient with a timely diagnosis and a
multidisciplinary approach to promote the search of possible complications associated that can help reduce the burden of the disease. It also gives the family a chance to explore possible carriers of the virus and avoid perpetuating transmission in future generations.

CONCLUSIONS

Most of the patients in these series with HTLV-1 infection come from the Colombian Pacific region, mainly involving the indigenous and Afro-descendant population. However, it is not a disease exclusive to these populations, for which new diagnostic tools must be implemented according to the clinical findings to elevate clinical suspicion of this disease.

The patients collected with HTLV-1 infection in this study were classified in clinical manifestations by organ systems, finding predominantly dermatological manifestations that include scabies and infective dermatitis. The second group was respiratory manifestations with significant pulmonary parenchymal damage, with the subsequent possibility of opportunistic infection. Thirdly, a group of expression of autoimmune diseases is also widely described in the literature. So far no clinical manifestations suggestive of ATLL or HAM were found.

The intention of the study is to expand the possibilities of diagnosis of this infection, in order to provide the patient with a timely diagnosis and to promote the search for possibly detect potential complications to help reduce the burden of this disease.

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DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

IJ assisted in writing the manuscript, was responsible of translating and preparing the manuscript to send to the journal. JM was responsible for the collection of the patients, analysis the data and participated in the writing and editing of the manuscript. MG was responsible for the editing of the final manuscript and assisted with the epidemiology analysis. JR was responsible for the collection of the patients and editing of the final manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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