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Review

Infective dermatitis associated with human T-cell lymphotropic virus type-1, an underdiagnosed disease

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ABSTRACT

Infective dermatitis associated with human T-cell lymphotropic virus type-1 (HTLV-1) (IDH) is a severe form of chronically infected eczema occurring in early childhood, although very rarely cases have been reported in adults. Most of the cases are from Jamaica and Brazil and occur in individuals with low socioeconomic status. IDH is always associated with refractory Staphylococcus aureus or beta-hemolytic Streptococcus infection of the skin and nasal vestibules. Patients with IDH may develop other even more severe HTLV-1-associated diseases, such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) of early or late appearance and adult T-cell leukemia/lymphoma. In the context of the Brazilian experience, it has been observed that 54% of IDH patients exhibit the juvenile form of HAM/TSP while the estimated incidence of adult HAM/TSP is 3%. As there are no curative treatments for HTLV-1 infection (or vaccines) or most of its associated diseases, prevention of infection is fundamental, mainly by vertical transmission, as it is responsible for the development of IDH, infantojuvenile HAM/TSP, and ATL. Public measures to reduce this transmission must be implemented urgently. Furthermore, it is recommended, mainly in HTLV-1 endemic areas, to search for HTLV-1 infection in all patients with infected eczema, even in adults.

Introduction

Infective dermatitis was described as a new disease in 1966, in Jamaica, 14 years before the discovery of the human T-cell lymphotropic virus type-1 (HTLV-1), as a severe form of chronically infected eczema occurring early in childhood [1]. In 1990, it was linked to this virus and began to be named infective dermatitis associated with HTLV-1 (IDH) [2]. In 1998, the criteria for its diagnosis were well established [3].

HTLV-1 infection

The HTLV-1 was the first human retrovirus to be discovered. It was estimated in 2012 that this virus infects at least 5-10 million people worldwide [4], however, the true global prevalence is underestimated because many highly populated countries such as China, India, and Russia remain with ill-defined or undetermined HTLV-1 prevalences [5]. The areas where high endemicity was shown are the Southwestern region of the Japanese archipelago, parts of the Caribbean and its surrounding regions, foci in South America including areas of Colombia, French Guyana, Peru, and Brazil, some areas of intertropical Africa, the Middle East, and isolated clusters in Australo-Melanesia. The only HTLV-1 endemic region in Europe is Romania [4,5]. However, due to the intense immigration flows, cases of HTLV-1 infection have been reported in other European countries mainly in France, Italy, and Spain as well as in the United Kingdom [4]. HTLV-1 infection should be considered a global public health problem. HTLV-1 is a neglected virus predominantly affecting individuals of low socioeconomic status, and causing neglected diseases [6,7]. HTLV-1 infection is transmitted vertically (mainly through prolonged breast/chestfeeding), through sexual contact, and parenterally (through blood transfusion, organ transplantation, or sharing of contaminated sharp objects, i.e. equipment for injecting drug use) [4]. In addition, zoonotic transmission from non-human primates can occur, at least in African rural populations [4]. Besides IDH, this virus may cause other severe diseases such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), adult T-cell leukemia/lymphoma (ATL), and

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HTLV-1-associated uveitis (HAU). The estimated life risk among people living with HTLV-1 to develop these serious diseases is around 5% for ATL (with high morbidity and mortality) and 2% for HAM/TSP, with a higher risk in women than men [5].

Notwithstanding, due to the immune dysregulation caused by the virus, the individuals living with HTLV-1, including the patients with IDH, are more susceptible to other infections and parasitosis, such as scabies, superficial mycosis, strongyloidiasis, and bacterial skin diseases, in comparison to with persons without the HTLV-1 infection [6,8] Laboratory diagnosis of HTLV-1 infection is performed using screening tests, followed by confirmatory tests. The most used screening test is the enzyme-linked immunosorbent assay (ELISA). All samples that test positive in the ELISA must be submitted to confirmatory tests to rule out false positive ones and to distinguish between HTLV-1 and HTLV-2. Western blot and innogenetics line immunoassay (INNO-LIA) are the confirmatory tests most used. Since the viral particles of HTLV-1 have low infective capacity, this virus is not in the human body primarily in the form of free viral particles, as occurs in other retroviruses like HIV. Instead, it integrates its RNA converted into proviral DNA into the DNA of the infected cell, generally T lymphocytes in peripheral blood. Thus, another confirmatory test is to detect HTLV-1 by PCR amplification of the integrated provirus in the DNA extracted from the peripheral blood mononuclear cells (PBMCs) of the individual being tested [4]. As there are no curative treatments or vaccines for HTLV-1 infection and most of its associated diseases, prevention of transmission is essential. Breastfeeding constitutes an important route of transmission because it is the via of infection in IDH, juvenile HAM/TSP [6,9], and ATL cases [10]. Prevention of mother-to-child transmission of HTLV-1 was considered a priority in the global response to this virus by the PAHO/WHO [11]. Antenatal screening is implemented officially in Japan, Santa Luzia Island and some States of Brazil [12-14]. Avoidance of breast/chestfeeding for pregnant women living with HTLV-1 was only implemented nationally in Japan [15]. In Japan's Nagasaki Prefecture, antenatal HTLV-1 screening and formula feeding of babies of pregnant women who were living with HTLV-1 reduced transmission from 20% to 2.5% [16]. Therefore, a small proportion of babies exclusively fed with infant formula may acquire HTLV-1 infection, suggesting the possibility of other vias of vertical transmission, transplacental [17], or blood contamination in the birth canal.

There is a great impact on the quality of life of individuals living with HTLV-1, mainly when they have neurological manifestations [18]. Also, a higher prevalence of psychiatric/psychological problems is observed among them than in the general population. They may manifest signs of psychological distress, anxiety, sleep and psychosomatic disorders, suicide ideation, low self-esteem, and depression [19]. There is still no assessment in the literature of the psychological impact of HTLV-1 infection in IDH patients. However, we believe that this impact would be greater than in other individuals living with HTLV-1, because patients with IDH, in addition to their mothers, often have siblings living with HTLV-1 and sometimes with diseases related to the virus [20].

Epidemiology of IDH

IDH has been described, in order of frequency, in Jamaica, Brazil, Peru, South Africa, and Senegal [3,6,7,21,22]. Isolated cases have been found in Colombia, the Dominican Republic, French Guyana, Trinidad/Tobago, and Australia [23,24]. Cases from Brazil and Jamaica have been reported in the literature as occurring in patients with low socioeconomic status [3,6]. In Japan, where the frequency of HTLV-I infection is high, only three cases of IDH have been reported [25]. In Brazil, most known cases were from the State of Bahia in the Northeast of Brazil [6]. A few cases have also been described in Rio de Janeiro, Rio Grande do Sul, and São Paulo [6,26,27]. Bittencourt and her group probably found more Brazilian cases of IDH in Bahia because this state is one of the most endemic regions for HTLV-1 in Brazil. Furthermore, in this state, projects are designed to study IDH [6,9].

Table 1
Frequency and distribution of lesions in 42 patients with infective dermatitis associated with HTLV-1

Areas involved	(%)
Scalp and retroauricular areas	100
Neck	88.0
Axillae	83.3
Groin	78.6
Paranasal skin	71.4
Ears	71.4
Torax	64.3
Abdomen	62.0
Antecubital and popliteal fossae	57.1
Eyelids	57.1
Forehead	54.8
Perioral region	50.0
Umbilicus	40.8
Limbs	35.7
External genitalia	33.3
Buttocks	16.6

The mean age at onset of IDH in Bahia, Brazil, is 2.6 ± 2.4 years (range, 2 months-11 years) [6], but in other countries, the mean age at onset of IDH is higher [3,7,21]. It may also begin in adulthood [8]. The mean age at complete disappearance of disease is 15 years (range, 10-20 years), but infrequently it may persist until at least 23 years of age [6]. A significant predominance of IDH in females exists [3,6], but this is not observed in Peruvian cases [7].

Clinical aspects

IDH is associated with a refractory, *Staphylococcus aureus* or beta-hemolytic *Streptococcus* infection of the skin and nasal vestibules [28]. *Staphylococcus aureus* infection is much more prevalent in IDH lesions than beta-hemolytic *Streptococcus* [6,21,22]. Its onset is usually in the form of rhinitis. It appears as a severe chronic eczema always involving the scalp and retro auricular areas (Figure 1a, b) and, more frequently, neck and axillae [3,6]. Table 1 shows the distribution and frequency of the lesions in 42 IDH cases in Bahia, Brazil [6]. The lesions were malodorous, erythematous-scaly, and exudative, covered with adherent yellowish crusts (Figure 1a). The lesions were disseminated in 83% of the cases. Very extensive lesions involving several adjacent regions are observed in cases with prolonged disease (Figure 1c). It is a disease with high morbidity. In addition to the erythematous, scaly, and crusty lesions, the patients may present pustules, erythematous-scaly papules, follicular-like papules, and retro-auricular fissures [6]. Rhinorrhea and crusting in the nostrils (Figure 1c) are common findings but may be missing [6,21]. Patients complain of pruritus. However, it is not as intense as in atopic dermatitis. Blepharoconjunctivitis is found in around 57% of cases [6]. Additional clinical features include anemia, elevation of erythrocytic sedimentation rate, hyperimmunoglobulinemia, elevated CD4 count, CD8 cell count, and CD4/CD8 ratio [3,21]. The cases in KwaZulu Natal, South Africa are described as less infected and more inflammatory in contrast to cases in Senegal and individuals of Black African descent in Bahia, Brazil [21]. A constant complication of IDH is scabies, including, less frequently, Norwegian scabies [6]. There is an association between HTLV-1 and scabies, and in IDH patients the presence of skin barrier breakdowns favors the entry and proliferation of this parasite. It is known that scabies may promote the growth of *Staphylococcus aureus* and *Streptococcus pyogenes* causing

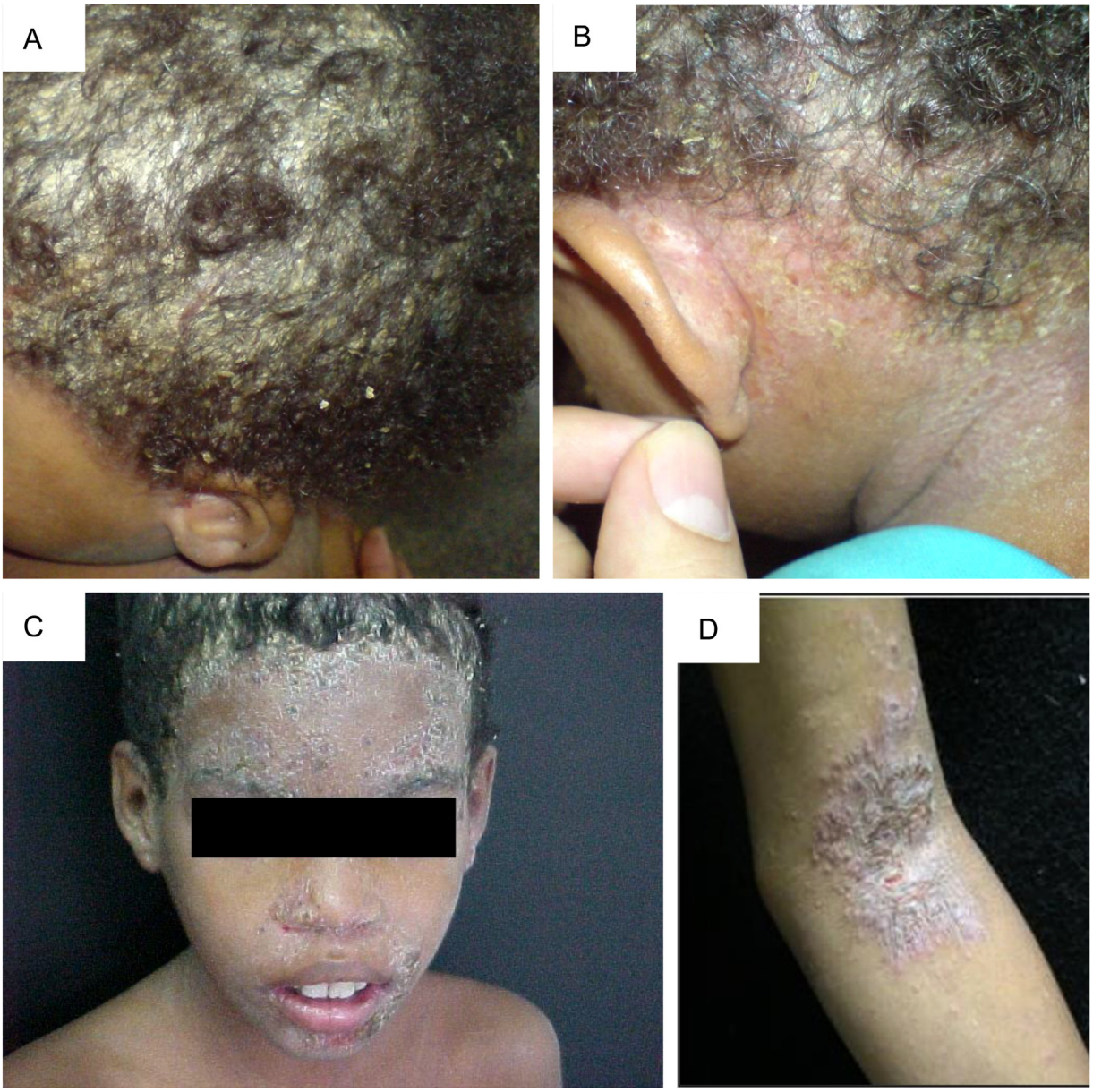

Figure 1. Cutaneous manifestations of IDH. (a) A three-year-old female child with a scaly and erythematous lesion on the scalp covered by adherent yellowish crusts. (b) A female child with an extensive erythematous-scaly-crusty lesion involving the scalp, retro auricular area, and neck. (c) An erythematous-scaly-crusty lesion on the scalp, ears, forehead, eyebrows, nose, and perioral area. Crusting on nostrils. (d) An erythematous-scaly-crusty lesion on the left antecubital fossae.

superinfection in animals and in vitro [29]. Therefore, it may have some influence on the maintenance of IDH.

In 2010, it has been proposed a modification in the main criteria previously established for the diagnosis of IDH [6,8]. According to the first main criteria of La Grenade et al. [3], the areas affected in IDH are the scalp, axillae and groin, external ear and retro auricular areas, eyelid margins, paranasal skin, and the neck, without reference to the frequency of the involved regions. In the modified criteria, it was emphasized that involvement of $\geq$3 of the sites is required, including involvement of the scalp and retro-auricular areas (Supplementary Table 1). As crusting of the nostrils was absent in some patients [6,21] and sometimes appeared only during subsequent relapses, its presence was not considered an obligatory factor for diagnosis. However, it represents, when present, an important criterion. Furthermore, rhinorrhea should not constitute an essential criterion for diagnosis because it is a common manifestation in children with several other diseases. Nevertheless, the relapsing nature of the disease, not present in the original main criteria, is a characteristic aspect of IDH. Thus this finding must be considered indispensable for diagnosis. On the other hand, the criterion requiring onset in early childhood was no longer valid because IDH may begin later in childhood or adulthood [30]. In seronegative patients with the classic characteristics of IDH, PCR to detect HTLV-1 provirus integration in PBMCs can be performed to clarify the diagnosis [6].

Differential diagnosis

The manifestations of IDH may overlap with other dermatological diseases. IDH should be differentiated from other types of eczema, such as atopic and seborrheic dermatitis. It is more frequently misdiagnosed with atopic dermatitis [7,31]. A positive serologic test for HTLV-1 is not enough to diagnose IDH because atopic dermatitis may appear in 14% of the children living with

HTLV-1 as well as seborrheic dermatitis in 25% [3,32]. In childhood atopic dermatitis, occurring after 2 years of age, the lesions partially resemble IDH; however, in IDH, the lesions are more exudative, infected, and exuberant, and nasal crusting is frequently found. Lesions in the antecubital (Figure 1d) and popliteal fossae may sometimes hamper the differential diagnosis of atopic dermatitis [6]. In seborrheic dermatitis, the lesions are erythematous and scaling and less infected than those found in IDH. On the other hand, rhinitis and a papular rash may be present, features that are not found in seborrheic dermatitis. Another relevant difference is the presence of pruritus in IDH, which is practically nonexistent in seborrheic dermatitis. The squamous are oily, and *Pityrosporum* is often found. Moreover, IDH responds well to treatment with sulfamethoxazole/trimethoprim [8]. It is essential to consider that more intense pruritus in IDH may be caused by the frequent association with scabies [8].

Histopathology

Histopathologic aspects in IDH are not specific, but the histopathologic study is essential for differential diagnosis with other diseases. Microscopically, acanthosis, hyperkeratosis or parakeratosis, spongiosis, a slight epidermotropism of lymphocytes, and crusting are found. In some biopsies, a psoriasiform acanthosis and less frequently the presence of Munro's abscess may simulate psoriasis (Supplementary Figures 1a, b). A more marked epidermotropism and obliteration of the basal layer by T lymphocytes may mimic early mycosis fungoides (Supplementary Figure 1c). A slight to moderate infiltration of typical lymphocytes in the dermis is observed, predominantly consisting of typical CD8+ T lymphocytes without cytotoxic granulations. The lymphocytes are exclusively or predominantly CD8+ with a low proliferative index > 5% (Ki-67) [33].

Development of other HTLV-1-associated diseases in individuals with IDH

It has been observed that individuals with IDH may develop HAM/TSP, a severe and disabling form of myelopathy that generally occurs in adulthood. La Grenade et al. described the first two cases of IDH that developed HAM/TSP [3]. Later, Araujo et al. reported five cases of juvenile HAM/TSP in Brazil, three of them associated with IDH [26]. Twenty of 37 (54%) IDH patients followed up in Bahia developed juvenile HAM/TSP before 19 years of age [9]. The similarities between the immunologic response observed in patients with IDH and in patients with HAM/TSP (an exaggerated Th1 type immune response) would appear to suggest that IDH constitutes a risk factor for the development of juvenile HAM/TSP [34].

There have been four isolated reports on the appearance of ATL during the evolution of IDH [35]. Besides, 37% of ATL cases with skin involvement observed in Bahia, Brazil, reported a history of severe eczema in childhood, very suggestive of IDH [36]. Atypical lymphoid cells, including flower cells, were observed in 17% of a cohort of 30 IDH children and adolescents. The percentage of flower cells ranged from 2 to 3% in these patients, and they were not considered to be smoldering ATL because they do not have cutaneous lymphoma or ≥5% of atypical cells in peripheral blood [37]. Flower cells are generally found in acute and occasionally in chronic ATL [38]. These data suggest that IDH constitutes a risk factor for the development of ATL.

Pathogenesis

HTLV-1 infects mainly CD4+ T lymphocytes and integrates its provirus into the genome of the infected cell. To establish the infection and to survive, the HTLV-1 tries to increase the number of infected cells in the human body rather than to produce new viral particles that have low infection capacity. The proviral load (PVL) has been demonstrated to be a relevant parameter to monitor HTLV-1 infection. PVL refers to the number of HTLV-1 infected cells in the PBMCs. Assuming that each infected cell contains only one copy of the HTLV-1 provirus integrated into its DNA, the PVL is quantified by the number of HTLV-1 proviruses integrated into human DNA (extracted from PBMCs) per total number of human cells using quantitative PCR [39]. PVL is the result of the balance between proliferation and lysis of those infected cells by the action of the host immune system. High PVL is considered a risk factor for the development of HTLV-1-associated diseases such as ATL and HAM/TSP [40]. In IDH, PVL was shown to be higher than in juvenile asymptomatic individuals of a Brazilian cohort and it did not increase with the comanifestation of HAM/TSP [39]. Indeed, HAM/TSP was not necessarily developed in those IDH patients who initially presented high PVL, suggesting that high levels of PVL are not a risk factor for the development of HAM/TSP in IDH patients. Furthermore, PVL does not decrease after IDH remission indicating that the disappearance of the dermatologic manifestations may be related to an acquired capacity to control the bacterial infection more than a reduction of the infected cells [39]. In this sense, higher PVL after IDH remission may favor the early development of ATL.

HTLV-1 promotes the increase of infected cells within the human body through different mechanisms, mainly: (i) virologic synapses, where the HTLV-1 provirus and other viral products are transferred from an infected cell to a noninfected cell generating different clones with different provirus integration sites in the human DNA and (ii) mitotic division that results in identical infected cells with the same provirus integration site [41]. In this setting, another relevant parameter in the pathogenesis of HTLV-1 infection is the clonality pattern or clonality index [42] that informs about the number of different infected clones (that resulted from virological synapses) and the abundance of each clone (as the result of mitotic division) that constitutes a population of HTLV-1 infected cells. IDH and HAM/TSP present a polyclonal pattern of provirus integration of infected cells, which means a mixture of a multitude of different clones with different (or similar) abundance, but none of them predominant, while ATL is characterized by a monoclonal pattern of infected cells with a predominant (and neoplastic) clone with high proliferative capacity and highly abundant. In seven Brazilian IDH patients with a percentage of abnormal T cells or flower cells ranging from 2 to 3%, a monoclonal pattern of proviral integration was observed when investigated by inverse-long PCR (unpublished results). These patients were not considered as smoldering ATL because they did not have skin lymphoma or ≥5% of atypical cells in peripheral blood and all of them presented T-cell polyclonality. The presence of a clonal pattern of proviral integration without disease is considered a pre-ATL condition. Using a whole genome sequencing approach, the clonality pattern and CI of infected cells in IDH were investigated in deep [43]. It has been shown that higher PVL observed in IDH patients was related to a high abundance of infected cells as the number of different clones was similar to that observed in individuals living with HTLV-1 without IDH [43]. It may indicate that IDH patients may be less capable of controlling infected clone abundance. Interestingly, the presence of the largest clones in IDH patients was independent of the genomic environment of the proviral insertion site [43], suggesting that the proliferation of infected T cells was stimulated by an external factor, probably a bacterial infection.

Studies have attempted to associate factors of the host with infection outcomes. Indeed, in Bahia, Brazil, familial clustering of IDH and HAM/TSP was observed in 15 of 28 families with at least one child with IDH, 93% in two generations [20]. Except for two, all

the mothers with HAM/TSP had at least one child with myelopathy, generally associated with IDH. Certain haplotypes of associated human leukocyte antigen (HLA) are described in the literature to predispose to the development of ATL and HAM/TSP in the Japanese population. On IDH only a descriptive work documented two Jamaican IDH patients, one mother and her child sharing a class I1 haplotype, A29Cw4B7 DRB1*DQB1*(1101-0301) that was previously associated with Japanese HAM/TSP patients [44].

Expression of proviral genes has also been associated with the maintenance of HTLV-1 proviral load [45]. The products of the genes tax and HBZ of the pX region have been associated with the pathogenesis of ATL and HAM/TSP and their role and dynamics of expression have been the subject of several studies in recent years [46,47]. To our knowledge, no data is about the pathogenic relevance of the products of the pX region genes in IDH and this aspect must be further addressed.

Management

As there is no treatment or vaccine for HTLV-1 infection, prevention of transmission is fundamental. Global implementation of prenatal screening for HTLV-1 and governmental public support for pregnant women living with HTLV-1 are urgently needed [48]. Patients with IDH must have, in addition to the dermatological examination, a complete medical examination, with laboratory assessments, including search for *Strongiloides stercorales* and HIV serology. It is also important to test parents and siblings for HTLV-1. They should also be monitored clinically, and adequately informed about transmission-preventive measures.

Since IDH is always associated with bacterial infection, it responds well to antibiotics but there is a high recurrence rate. Oral trimethoprim-sulfamethoxazole (40 mg/kg q24h of sulfamethoxazole and 8 mg/kg q24h of trimethoprim) is a good treatment choice because of its effectiveness and low cost [22,23]. According to the relapses of the disease, the therapy should be repeated, but generally in smaller doses. As scabies infection is frequent in these patients, treatment should always be considered at admission and during follow-up. Parents and siblings should also be treated during follow-up. Antihistamine drugs, topical corticosteroids, and emollients are also recommended. These patients should be followed up with clinical and neurological exams. They should be periodically tested for strongyloidiasis, parasitosis frequently present in individuals living with HTLV-1 association may constitute a predisposing factor for the evolution to ATL since it leads to clonal expansion of T lymphocytes [43]. Strongyloidiasis is often asymptomatic and should be investigated and treated because adequate treatment can reverse the clonal expansion.

Adulthood IDH

Since 2001, 12 cases of adulthood IDH have been published, 11 in Latin America and one in Australia, four associated with HAM/TSP [24,30]. In 2020, a study including 12 adult patients with IDH in Bahia, Brazil, followed for up to 18 years compared the clinicopathological aspects of both forms of IDH (adult vs juvenile) in the same dermatologic unit and concluded that the characteristics of the adulthood IDH cases are similar to those of juvenile IDH [30]. Female predominance also occurred in the adult form, and the features and distribution of lesions were similar, with constant observation of lesions on the scalp and retro-auricular regions. However, unlike the juvenile form, lesions were found on the ankles and inframammary folds. In the juvenile form, inframammary involvement only occurs when female children reach puberty and begin to have inframammary folds. Very extensive lesions involving several adjacent regions, as already mentioned in the juvenile form, have also been observed in the adult form. The chronic relapsing characteristic of IDH and the frequency of erythematous-squamous papules, follicular papules, retroauricular fissures, and blepharoconjunctivitis were also similar to those described in the juvenile disease. The frequency of association with HAM/TSP was also high (50%), similar to that observed in the juvenile form (54%). In contrast to the juvenile form, in which IDH always precedes HAM/TSP, in three adult patients, IDH appeared after the development of myelopathy. High levels of HTLV-1 proviral load were also detected in this form of IDH. It was concluded that the diagnostic criteria and treatment used for juvenile disease perfectly apply to adult IDH [30].

Conclusions

Infective dermatitis associated with HTLV-1 is a severe form of chronically infected eczema that occurs in childhood and less frequently in adults. It dramatically impacts the patient's quality of life and represents a risk factor for developing HAM/TSP of early or late appearance and ATL. Since there are no curative treatments (or vaccines) for HTLV-1 infection and for most of its associated diseases, prevention of vertical transmission is essential to control the development of IDH and juvenile HAM/TSP cases and ATL. We believe that most cases of IDH are underdiagnosed due to the medical community's lack of awareness. Additionally, the majority of IDH-published cases, including those diagnosed in Bahia, Brazil, did not have a previous diagnosis of their cutaneous disease or were previously considered cases of atopic dermatitis [7,31,35]. It should be mandatory, mainly in endemic areas, to search for HTLV-1 infection in all patients with infected eczema, even in adults.

Declarations of competing interest

The authors declare that there are no conflicts of interest.

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Ethical approval

The Research Ethics Committee of the Professor Edgard Santos Teaching Hospital of the Federal University of Bahia, Brazil approved this study protocol (number 3.002408).

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Author contibutions

ALB and LF conceived the idea of this review, wrote the manuscript and contributed equaly to this work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107058.

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