Clinical and Epidemiologic Profile of Cutaneous Leishmaniasis in Colombian Children: Considerations for Local Treatment

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Abstract. Treatment alternatives have seldom been evaluated in children with cutaneous leishmaniasis (CL). We examine the clinical/epidemiological profile of children with CL considering international guidelines for local treatment. Descriptive analyses were conducted using International Center for Medical Research and Training (CIDEIM) case reports of parasitologically diagnosed patients ≤ 14 years of age from 2004 to 2010. Eligibility for local treatment based on World Health Organization/Pan American Health Organization (WHO/PAHO) criteria was determined. Among 380 children, 90% presented lesions of < 3 months duration, 54% presented single lesions < 30 mm in diameter, and 45% were ≤ 5 years old. Lesions on the head and neck were more frequent among children 0–5 years, and lesions below the head/neck were more frequent among 11- to 14-year-old children ($P = 0.004$). Using PAHO and WHO criteria, 26% and 53% of children, respectively, were eligible for local treatment. Recommended local treatments for New World CL have potential but limited applicability in children. Individual risk–benefit assessment and effectiveness data in children may increase eligibility.

INTRODUCTION

Children have become increasingly vulnerable to cutaneous leishmaniasis (CL) as a result of transmission in domestic and periurban settings, but treatment alternatives have seldom been considered or evaluated for this population. The few studies that have been conducted have shown that children with CL have a lower response rate to pentavalent antimonial compounds and a significantly higher elimination rate of antimony compared with adults.^{1,2} These circumstances coupled with the logistic, social, and economic barriers to access and adherence to 20 days of intramuscular injections limit the effectiveness of antimonial drugs, which remain the first-line treatment of CL in children. Miltefosine has recently been shown to be non-inferior to meglumine antimoniate in the treatment of pediatric CL in Colombia,³ and its efficacy in children is corroborated by clinical trials in populations where *Leishmania guyanensis* and *L. braziliensis* are endemic in Brazil.^{4,5} However, guidelines for the treatment of children with CL have not yet been implemented and access to the pediatric formulation of miltefosine is limited. Notably, neither data nor guidelines are available for treatment of children under 2 years of age with CL with any antileishmanial drug.

Prevalence and incidence data for CL in children are scarce and restricted to a few endemic foci where studies were conducted over a decade ago. Reported prevalence in children under 15 years of age has varied from 13% to 35% in endemic areas in Brazil, Venezuela, and Argentina.^{6–8} In Colombia from 2003 to 2009, annually reported cases ranged from 7,382 to 18,155, with from 10.3% to 26.6% of cases being children under 15 years of age (Public Health Epidemiologic Surveillance Group of the Ministry of Health and Social Protection and Colombian National Institutes of Health).

High prevalence of CL in children is generally considered to signal domestic transmission, which has expanded into the household settings of rural communities and periphery of urban centers in endemic areas throughout Central and South

America.^{9–12} Current and high-quality information on CL in children is needed to effectively address the unmet therapeutic needs of this vulnerable population.

In 2010, the World Health Organization (WHO) Expert Committee on Leishmaniasis recommended the inclusion of local and topical treatments among the acceptable therapeutic alternatives for New World leishmaniasis after a reassessment of the risk/benefit relationship of the use of toxic systemic therapy for all presentations of CL. This recommendation was based on (1) the low risk of mucosal involvement and the clinical efficacy of treatment of mucosal disease when opportunistically detected versus the potential of life-threatening adverse effects of first-line systemic treatments (antimonials and pentamidine) and (2) the feasibility of effective local treatment of mild localized lesions, which constitute the majority of cases.¹³ In 2011, a Pan American Health Organization (PAHO) Expert Committee on leishmaniasis included the recommendation of local treatment within the regional guidelines for the treatment of leishmaniasis in the Americas and defined criteria that restricted local treatment to single, mild lesions not involving the face or joints. However, neither WHO nor PAHO recommendations included considerations or criteria for local treatments in children.

This study describes the clinical and epidemiological profile of the pediatric population with leishmaniasis diagnosed and referred for treatment by a national referral center in the southwest region of Colombia from January of 2004 to December of 2010 and evaluates the feasibility of treating children with currently available local therapies based on the recently revised guidelines of WHO and PAHO.

MATERIALS AND METHODS

Study design. This retrospective study was conducted using a database of clinical records of patients diagnosed from January of 2004 to December of 2010 at the clinical referral centers of the Centro Internacional de Entrenamiento e Investigaciones Medicas (CIDEIM) in the cities of Cali and Tumaco. Cali is the principle urban center in the southwestern region of Colombia, and patients from this region are referred here for diagnostic evaluation and medical attention. The

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municipality of Tumaco, on the Pacific Coast of the state of Nariño, is an endemic area for CL. Most patients diagnosed at the clinical center in Tumaco are residents of rural areas of this municipality.

Strategy. The medical database containing all the information registered in the medical records was filtered to identify children from 0 to 14 years of age. Afterward, missing data were manually sought in the patient medical charts and completed or excluded from the analysis as established by predetermined exclusion criteria.

Eligibility criteria. Patients who met the following eligibility criteria were included: male and female children from 0 to 14 years of age having parasitological diagnosis of leishmaniasis and date of initial consultation from January of 2004 to December of 2010. Exclusion criterion was incomplete clinical history.

Parasitological diagnosis. Etiologic diagnosis of leishmaniasis was established by direct smear, culture, or skin biopsy. Diagnosis and strain identification are routinely performed at CIDEIM clinical centers as previously described.¹⁴ Parasite species was identified using monoclonal antibodies and/or isoenzyme analysis.^{15,16}

Criteria for local therapies. A retrospective clinical assessment was conducted to determine the proportion and epidemiologic characteristics of children meeting WHO and PAHO criteria for management with local treatment using thermotherapy or intralesional injections of pentavalent antimonials. These local therapies are now a treatment option for CL in the New World after risk-benefit evaluation based on either WHO or PAHO criteria developed specifically for the Latin American region. Both WHO and PAHO criteria consider the number, size, and localization of lesions but differ with respect to the number and size limits of cutaneous lesions that are eligible for local treatment. We, therefore, applied both and compared the outcome. WHO criteria are fewer than four lesions; lesions < 5 cm in diameter; no potentially disfiguring or disabling lesions (face, joints, toes, and fingers); no immunosuppression; and feasibility of follow-up. PAHO criteria are a single lesion having an area of up to 900 mm² or diameter ≤ 3 cm (excluding lesions located on the head or joints).

Statistical analysis. Descriptive statistical analysis of demographic and clinical variables for children and their potential eligibility for local therapies was performed using STATA software, version 10.0. The study protocol was reviewed and approved by the CIDEIM institutional ethical review board.

RESULTS

Patients. Among 2,629 patients consulting for CL during the 7-year period (January of 2004 to December of 2010), 483 patients (18.4%) were children between 0 and 14 years of age. Of these children, 382 patients had a parasitologically confirmed diagnosis of leishmaniasis. Case histories of a total of 380 children were analyzed. Two cases were excluded because of incomplete data.

Demographic characteristics. The demographic characteristics of children with CL are summarized in Table 1. Notably, 44.5% of the children were 5 years of age or younger; 60 children (16%) were under 2 years of age. Although three ethnicities were represented, the predominant ethnic identity was Afrocolombian (42.4%); 22% of children had publically

TABLE 1
Demographic and clinical characteristics of patients by study site

	Cali (N = 41; %)	Tumaco (N = 339; %)	Total (N = 380; %)
Sex			
Male	28 (68.3)	171 (50.4)	199 (52.4)
Female	13 (31.7)	168 (49.6)	181 (47.6)
Age (years)			
0–5	16 (39.0)	153 (45.1)	169 (44.5)
6–10	13 (31.7)	99 (29.2)	112 (29.5)
11–14	12 (29.3)	87 (25.7)	99 (26.0)
Ethnic identity			
Mestizo	21 (51.2)	114 (33.6)	135 (35.6)
Afrocolombian	18 (43.9)	143 (42.2)	161 (42.4)
Indigenous	2 (4.9)	78 (23.0)	80 (21.0)
No data	–	4 (1.2)	4 (1.0)
Number of lesions			
1	20 (48.8)	185 (54.6)	205 (54.0)
2–3	11 (26.8)	106 (31.3)	117 (30.8)
4–5	9 (22.0)	33 (9.7)	42 (11.0)
≥ 6	1 (2.4)	15 (4.4)	16 (4.2)
Duration of oldest lesion (months)			
< 2	14 (34.1)	165 (48.7)	179 (47.1)
2–3	19 (46.3)	145 (42.8)	164 (43.2)
4–5	4 (9.8)	13 (3.8)	17 (4.5)
> 5	4 (9.8)	16 (4.7)	20 (5.2)

subsidized healthcare coverage, and only 1.6% of children was insured through the Colombian contributory social security system. The remaining 78% lacked any health insurance. Sex distribution by age (Figure 1) showed boys and girls under 10 years of age to be comparably affected, whereas males were more frequently affected than females in the 11- to 14-year age range.

Clinical presentation. Among 380 children included in this analysis, 5 children (1.3%) presented concomitant mucosal involvement. All mucosal disease was secondary to a cutaneous lesion affecting the nose or lips by proximal extension. No cases of exclusive mucosal disease or visceral leishmaniasis were identified.

Most children (54%) presented a single lesion, with a median of one lesion per patient and a range of one to nine lesions. The time of evolution of lesions at diagnosis was less than 3 months in 90.3% of patients; the median was 1.5 months, and the range was 0.2–24 months. Table 2 summarizes the clinical characteristics of the total number of lesions by study site. A total of 785 lesions were evaluated; 556 lesions (70.8%) had a diameter ≤ 30 mm, and the median area was 195 mm². Ulcers were the most common lesion type (92.6%) without presence of either regional lymph node (93.4%) or lymphatic tract involvement (97.8%).

Children from 0 to 5 years of age presented lesions located principally on the head and neck (52%) (Figure 2), which is in contrast with older children of 11 to 14 years of age, whose lesions were predominantly below the head and neck (62.6%; $P = 0.004$). Differences in lesion localization by age were corroborated by the decrease in lesions on the head and neck and increase of lesions on trunk and limbs with age. No relationship between the number of lesions and age was detected.

Diagnostic test results and species identification. Results of direct smears were available for 363 patients; 91% were positive. Only one case was diagnosed by skin biopsy. Cultures of lesion aspirates were conducted for 251 patients; 80% were positive. Strain identification was undertaken for 136 cases. The predominant species was *L. (Viannia) panamensis* (96.3%) followed by *L. (Viannia) braziliensis* (2.2%), and in

FIGURE 1. Sex of CL patients in relation with age showing increased proportion of males among patients ≥ 10 years of age. Significant differences were seen when sex proportions were compared by age group (i.e., 0–5, 6–10, and 11–14 years old; $\chi^2 = 9.59$, $P = 0.008$).

2 of 136 strains, identification based on monoclonal antibodies was limited to the subgenus *Leishmania* (*Viannia*).

Assessment of eligibility for treatment with local therapies. Among 380 children, only 26% and 53% fulfilled PAHO and WHO criteria, respectively, for local treatment. The number and proportion of potentially eligible patients for local therapies are summarized in Figure 3. Because recommendations are based on risk–benefit considerations, they may be adjusted according to the age and circumstances of the patient (i.e., infant versus pre-adolescent, access to local treatment and follow-up, and expertise of the treating health worker). Taking into account the difficulties of local treatment in infants, who are unable to cooperate with the procedure, we evaluated the addition of the criterion of age above 2 years for the application of currently available local therapies in children. Application of the criterion of age ≥ 2 years, in addition to criteria

included in PAHO and WHO guidelines, reduced the proportion of children with CL who would be eligible for local therapy from 26% and 53% to 22% and 30%, respectively.

DISCUSSION

Several drugs and treatments that clinically resolve the lesions of CL are available, but they are accessible to or effective in only a portion of affected populations. Therapies that address the needs and limitations of the different segments and circumstances of the populations are needed to reduce the burden and consequences of CL. Children with CL present a constellation of therapeutic challenges. These challenges include greater pathogenicity of *Leishmania* infection in younger patients compared with adults,¹⁷ the propensity for lesions on the face, their remote rural residence and their dependency for access to medical attention on adults who commonly are struggling to provide basic needs for multiple children, and the limited pharmacologic data on and likelihood of distinct pharmacokinetics and pharmacodynamics of antileishmanial drugs in children.

Theoretically, local treatment could overcome most or all of these limitations. However, our examination of clinical presentation of children who have acquired CL in the southwestern region of Colombia indicates that they are largely ineligible for local treatments recommended by recent WHO and PAHO guidelines (Figure 3). If children under 2 years of age are deemed ineligible, the proportion is even lower. These international guidelines are based on the medical requirements and risk–benefit considerations of the currently recommendable local treatments: thermotherapy, intralesional pentavalent antimonial drugs, and topical formulations of paramomycin. The probable involvement of *Leishmania* of the *Viannia* subgenus in the majority of cases in most of Latin America and the association with mucosal disease influence

TABLE 2
Characteristics of lesions by study site

	Cali (N = 101; %)	Tumaco (N = 684; %)	Total (N = 785; %)
Lesion size (cm)*			
≤ 3	44 (43.6)	512 (74.8)	556 (70.8)
> 3	57 (56.4)	172 (25.2)	229 (29.2)
Lesion size (cm)*			
< 5	97 (96.0)	680 (99.4)	777 (99.0)
≥ 5	4 (4.0)	4 (0.6)	8 (1.0)
Type of lesion			
Ulcer	74 (73.3)	653 (95.5)	727 (92.6)
Plaque	9 (8.9)	8 (1.2)	17 (2.2)
Nodules	2 (2.0)	12 (1.7)	14 (1.8)
Papules	7 (6.9)	6 (0.9)	13 (1.6)
Other	9 (8.9)	5 (0.7)	14 (1.8)
Location			
Head and neck	29 (28.7)	195 (28.5)	224 (28.5)
Upper limbs	34 (33.7)	223 (32.6)	257 (32.8)
Lower limbs	22 (21.8)	191 (27.9)	213 (27.1)
Trunk	16 (15.8)	75 (11.0)	91 (11.6)

*The greater vertical or horizontal diameter.

FIGURE 2. Localization of lesions in relation with age showed an inverse relationship between the frequency of lesions on the head and neck and the trunk and limbs. Lesions located on the head and neck were more frequent in the 0- to 5-year age group, whereas lesions located below the head and neck (trunk and limbs) were predominant in the 11- to 14-year age group ($\chi^2 = 11.23$, $P = 0.004$).

the risk-benefit assessment of eligibility for local therapy. Hence, only 26% of 380 children with CL in this study would have been eligible for local treatment based on PAHO guidelines for treatment of leishmaniasis in Latin America. Furthermore, the need for restraint and/or sedation of infants receiving thermotherapy or intralesional injections, the requirement of specialized equipment and experienced medical professionals, and the potential risk of local adverse events in infants and young children, which constituted a large proportion of the cases ($44.5\% \leq 5$ years of age) in children diagnosed over a 7-year period by our national reference center, impose constraints on the routine use of these local treatments for pediatric CL. Infants and children under 2 years of age present a particularly dramatic situation, because there is no recommended treatment of CL in this age group. Pentavalent antimonial treatment is not generally accepted, unless lesions are severe or involve mucosa.

In the Americas, risk of mucosal involvement has driven the recommendation and acceptance of toxic systemic treatment. However, the indefinite persistence of *Leishmania* after treatment and the asymptomatic presence of parasites in mucosal tissues of patients with active cutaneous disease,¹⁸⁻²² a history of CL, or even asymptomatic infection prompted reassessment of the pathogenesis and risk of mucosal disease.²² The therapeutic goal of clinical resolution of cutaneous lesions is accompanied by reduction of parasite burden but now recognized to be independent of elimination of infection.

The epidemiologic profile of children from the Colombian Pacific Coast with CL described in this study showed that children younger than 5 years were the most frequently affected and more vulnerable to develop lesions on the head and neck. These findings are similar to those findings reported in children by other studies in Brazil that hypothesized that the higher proportion of lesions localized on the

face/neck and upper limbs in children could be related with the feeding hours of phlebotomines, which are more active at the time when young children are sleeping and these body parts are more exposed to vector feeding.²¹⁻²⁴ Human odor, CO₂, or other elements in the breath could attract vectors into the house and thereby contribute to the higher proportion of young children affected in the domestic setting.²⁵

Treatment is the pillar of disease management and control of CL. No single drug or approach has proven suitable for all patients or circumstances. International guidelines define criteria and standards that seek to optimize benefit and minimize risk of recommended treatments based on available evidence. These guidelines provide the bases for national public health policy and acquisition of essential medicines; however, individual medical decisions may consider the circumstances and risk-benefit relation of each case. Disease severity, feasibility of access and adherence, risk of severe adverse affects, pharmacologic considerations in the very young and old, and the parasite involved all factor into the suitability of a treatment in different target populations. The evaluation as well as the development and design of effective treatments for CL require current and reliable information about the populations affected and targeted by particular interventions. The feasibility of using local therapies to treat children with mild CL is an important consideration, because antimonial drugs are more rapidly eliminated in children; also, the application of daily intramuscular injections is logistically unattainable for many families.² Miltefosine has been shown to be safe and effective in the treatment of New World CL in children³; however, the pediatric formulation is not widely available, and policies and measures for its appropriate use and management have not been implemented.

The reduced number and duration of treatments using thermotherapy or intralesional administration of meglumine

FIGURE 3. Eligibility of children with CL for local treatment. Number and proportion of children who (A) fulfilled PAHO criteria for management with local therapies and (B) met WHO criteria for local treatment. No differences in eligibility were detected when stratified by age group.

antimoniates offer advantages over systemic treatment with either antimony or miltefosine. Thermotherapy has proven efficacious in the treatment of CL in adults in Old and New World settings, with cure rates from 58% to 75% for CL caused by *L. braziliensis* or *L. panamensis* and from 69% to 73% for *L. tropica* and *L. major*.^{26–30} Tolerability of thermotherapy for young children, who can require multiple treatments to achieve clinical resolution, has not been evaluated. A recent study of intralesional treatment of CL in patients 12 years of age and older in Bolivia reported 70% efficacy and was considered an attractive therapeutic alternative for approximately 49% of patients having infections attributable to *L. braziliensis* who met the criteria of single lesions of less than 900 mm².³¹ Treatments with one to three applications of thermotherapy or intralesional antimonial drugs may prove more acceptable than 20 days of intramuscular injections, particularly if the discomfort of these procedures, which may not be well-tolerated by children or their parents, can be mitigated by local anesthesia. Nevertheless, the technical requirements and specialized capacities to adequately administer these local treatments limit feasibility in rural areas, where domestic transmission affecting children occurs and access to medical attention is difficult. Topical antileishmanial treatments containing paramomycin daily for 20 days have proven effective for the treatment of CL caused by *L. major*.^{32,33} Topical treatments that can be managed at the primary care level or even as home-based care could overcome many of the technical impediments for local treatment of CL in children. How-

ever, in addition to being an experimental formulation and hence, unavailable, the efficacy and effectiveness of paramomycin for New World CL have not been established.³⁴ This analysis of clinical presentation of New World CL in children and WHO and PAHO eligibility criteria for local treatment substantiate the dramatic, unmet challenge of treatment of pediatric CL.

Received December 30, 2012. Accepted for publication May 20, 2013.

Published online June 24, 2013.

Acknowledgments: The authors thank the dedicated health personnel in the municipality of Tumaco and the Department of Valle del Cauca and the research staff of the Centro Internacional de Entrenamiento e Investigaciones Medicas-CIDEIM (Internacional Center for Medical Research and Training), whose efforts over several years provided the database analyzed for this study. We also acknowledge and thank Dr. Victor Hugo Alvarez and the Public Health Epidemiologic Surveillance group of the Ministry of Health and Social Protection for access to national statistics of reported cases. The American Society of Tropical Medicine and Hygiene (ASTMH) and the American Committee on Clinical Tropical Medicine and Travelers' Health (ACCTMTH) assisted with publication expenses.

Financial support: Support for this study was provided in part by Swiss National Foundation Grant IZ70Z0-131421 and COLCIENCIAS Contracts 222951928964 and 222951928948.

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