

Pediatric Cutaneous Leishmaniasis in Turkey: A Retrospective Analysis of 8047 Cases

Abdullah Solmaz¹, İsa An², Ufuk Acar¹, Mustafa Aksoy¹

¹Harran University, Şanlıurfa, Turkey; ²Sanliurfa Training and Research Hospital, Şanlıurfa, Turkey

Corresponding author:

İsa An, MD

Sanliurfa Training and Research Hospital

Eyyubiye, Şanlıurfa, Turkey

is_an89@hotmail.com

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ABSTRACT Cutaneous leishmaniasis (CL) is common in the pediatric population, but there are only a limited number of studies focused on the clinical and epidemiological characteristics of patients in this age group. In this study, our objective was to investigate the epidemiological and clinical characteristics of pediatric subjects diagnosed with CL. A total of 8047 patients who had been diagnosed with CL between 2010 and 2021 in an endemic region were included in this retrospective study. The clinical and demographic characteristics such as age, gender, number, size, duration, location, and type of lesions and the administered CL treatments were recorded. In order to better understand the epidemiological and clinical characteristics of patients with pediatric CL (PCL), the study patients were divided into three groups according to their age (0-6, 7-12, and 13-18 years) and the clinical and epidemiological characteristics of these groups were compared. When patients with PCL were compared according to age groups, it was found that the highest number of patients were in the 13-18 age group. It was determined that the patients in the 6-12 age group had fewer lesions, that and the size of the lesions was smaller than the other groups. The disease duration was the longest in the 0-5 age group. The highest rate of nodular, ulcerated, and recurrent lesions was in the 13-18 age group, and the highest rate of papular lesions was in the 6-12 age group. Systemic pentavalent antimony therapy (IM or IV) was administered to 438 patients with PCL (5.44%), while intralesional pentavalent antimony therapy (IL) was administered to 7447 patients (92.54%). Patients receiving systemic therapy had larger lesions compared with patients receiving IL therapy and no treatment. The lesion duration was longer in patients who received systemic treatment, and the number of lesions was higher than those who received IL treatment. The highest rate of systemic treatment was in the 13-18 age group (43.8%). In conclusion, our study found that the intragroup comparison of the age group with the highest CL rate displayed similar clinico-epidemiological characteristics reported in previous studies conducted in the same region.

KEY WORDS: clinical, cutaneous leishmaniasis, epidemiological, pediatric, pentavalent antimony therapy

INTRODUCTION

Cutaneous leishmaniasis is a skin disease transmitted through the bite of the female sandfly and progresses with long-lasting nodulo-ulcerative lesions and heals with atrophic cicatrice (1). The clinical

and epidemiological characteristics of the disease change depending on several factors, including the parasites, host, and environment (2,3). CL continues to be an important public health problem in several

countries, particularly in developing countries (4,5). The incidence of CL is related to the ecological and seasonal properties of the regions and geographical distribution of the vector and its reservoirs (6,7).

CL is found in the tropical and subtropical regions between the 45th North and 32nd south parallels (1,8). Turkey is an endemic country for CL (2,9). According to the data of the Turkish Ministry of Health, almost half of the total 50381 CL cases which were diagnosed between 1988 and 2010 were reported in Şanlıurfa – a city in the Southeastern Region of Anatolia (10). A dramatic increase in CL cases was observed in Şanlıurfa after the Syrian civil war, which started in 2011, when millions of refugees took shelter in Turkey (11-13).

Although CL may present at any age, it is more common in the pediatric age groups. However, there are only a few studies evaluating the clinical and epidemiological characteristics of patients in these pediatric age groups (8,14,15). Aksoy *et al.* evaluated the clinical and epidemiological characteristics of 8786 patients with pediatric CL (PCL) who were diagnosed with CL between 1998 and 2014 in Şanlıurfa-Turkey(8). In this study, we investigated the epidemiological and clinical characteristics of patients diagnosed with PCL between 2010 and 2021.

PATIENTS AND METHODS

A total of 8047 patients who had been diagnosed with CL between 2010 and 2021 in an endemic region were included in this retrospective study. The clinical and demographic characteristics of the patients such as age, gender, number of lesions (1-5, 6-10, ≥11), size of lesions (1-5 mm, 6-10 mm, 11-15 mm, ≥16 mm), duration of lesions (1-16 weeks, 17-32 weeks, 33-48 weeks, ≥49 weeks), location of lesions (head/neck, body, upper extremities, lower extremities, generalized), type of lesions (nodular, papular, ulcerated, recurrent) and treatments administered due to the CL diagnosis (systemic (IM/IV pentavalent antimony treatment, intralesional (IL) pentavalent antimony treatment) were analyzed. In order to understand the epidemiological and clinical characteristics of patients with PCL, the included patients were divided into three age groups (0-6, 7-12, and 13-18

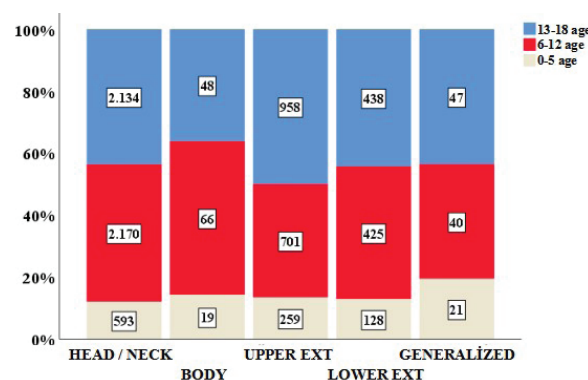


Figure 1. Distribution of pediatric cutaneous leishmaniasis cases by year.

years). The clinical characteristics such as the number, size, duration, location, and types of the lesions found in patients with PCL in these three age groups and the treatments administered due to CL diagnosis were compared.

CL was diagnosed by the observation of amastigotes in the microscopic examination of the Giemsa-stained smears, which were obtained from the skin lesions of patients. Our study was approved by the ethics committee (Approval Date / No: 08.06.2022 / 135984).

Statistical analysis

The study data were evaluated with the IBM SPSS Statistics v22.0 (IBM Corp.; Armonk, NY, USA) software package. Regarding the statistical analysis, mean ± standard deviation, median, minimum, and maximum values were used for continuous variables and number and percentage were used for the nominal variables. The normal distribution of the continuous variables was confirmed with the Shapiro-Wilk test, and the normal distribution charts, skewness, and kurtosis coefficient values were assessed together. The categorical variables were analyzed with the Chi-square test. The significance of the difference for continuous variables was analyzed with the Kruskal Wallis-H test, and the variable related to the difference was analyzed with the Dunn-Bonferroni test. For all analyses, $P < 0.05$ was considered statistically significant.

RESULTS

4084 out of 8047 included patients (50.8%) were men and 3963 were women (49.2%). The mean age was 11.35 ± 4.39 years. 6790 of patients (84.4%) were Turkish citizens, and 1257 (15.6%) were Syrian refugees. The mean diameter of the lesions was 9.98 ± 7.03 mm, while mean duration of the lesions was 13.69 ± 15.65 weeks. The mean number of lesions

Table 1. General characteristics of patients with pediatric cutaneous leishmaniasis

Age (years)	11.35±4.39
Number of lesions	1.90±1.92
Lesion diameter (mm)	9.98±7.03
Duration (weeks)	13.69±15.65

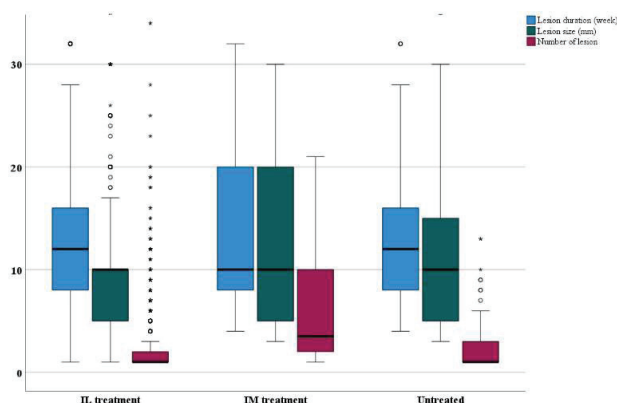


Figure 2. Distribution of lesion characteristics according to treatment status in patients with pediatric cutaneous leishmaniasis.

was 1.90 ± 1.92 . 89.9% of patients had 1-3 lesions, while 1.7% had 8 or more lesions (Table 1, Figure 1).

When patients with PCL were compared according to their age groups, it was found that the highest number of patients were in the 13-18 age group. The frequency of male patients was higher in all three age groups ($p > 0.05$). We determined that patients in the 6-12 age group had fewer lesions and smaller lesion sizes compared with the other groups ($p < 0.05$) (Table 2).

The most common location of the lesions was the head/neck region (60.9%). The second most affected region was the upper extremities (23.8%). Other involved regions were the lower extremities (12.3%), the body (1.7%), and generalized lesions (involvement of 2 or more regions) (1.3%). In the cases with generalized localization, the number of lesions was higher and the duration of disease was longer. The size of the lesions located in the lower extremities was larger. The most common lesion locations were the head/neck and body in the 6-12 age group and the upper and lower extremities in the 13-18 age group.

The most common clinical form found determined in patients with PCL was the nodular type (46.9%), which was followed by ulcerated (40.2%), papular (12.1%), and recurrent (0.8%) types. We found that the ulcerated and recurrent lesions were larger,

while papular lesions were small. As expected, the recurrent lesions had a long disease duration ($p < 0.05$). However, the nodular and ulcerated lesions were the clinical forms with the highest average number of lesions. The highest rate of nodular, ulcerated, and recurrent lesions was in the 13-18 age group, and the highest rate of papular lesions was in the 6-12 age group. Most of the recurrent lesions were located in the head/neck region, while the ulcerated lesions were found mostly in the lower extremities. The lowest rate of the clinical forms was observed in the 0-5 age group (Table 3).

We found that 438 patients with PCL (5.44%) had received systemic pentavalent antimony treatment (IM or IV), while 7447 patients (92.54%) had received intralesional pentavalent antimony treatment (IL). 162 patients (2.01%) had not been treated. Patients who had not recovered in the first cycle of the IL treatment had undergone the 2nd and/or 3rd cycles of the IL treatment. 4997 of the patients (62.10%) had achieved healing with only one cycle (8 injections). Regarding the remaining patients receiving IL treatment, 1559 (19.37%) required the 2nd cycle, and 891 of them (11.7%) required the 3rd cycle. Patients who received systemic treatment had larger lesions compared with patients receiving IL treatment or untreated patients. The duration and the number of the lesions were higher in patients receiving systemic treatment compared with the IL treatment group. It was found that the lowest rate of the 1st, 2nd, and 3rd cycles of the IL treatment was in the 0-5 age group. The highest rate of systemic treatment was in the 13-18 age group (43.8%). The rate of untreated patients was 31.5% and 53.7% in the 6-12 and 13-18 age groups, respectively (Figure 2).

DISCUSSION

Although it has been reported that CL is equally distributed among men and women, some studies have found that it was more common among women, and it was suggested that this finding depended on the tendency of women to present more frequently to physicians due to cosmetic concerns (1,16). Nezhad *et al.* investigated 7555 patients with PCL and found out that CL was more common among men

Table 2. The distribution of age, gender, and lesion characteristics of pediatric cutaneous leishmaniasis

Age (years)	Gender		Duration (weeks)	Number of lesions	Lesion diameter (mm)
	Male	Female			
0-5	523	497	13.75	2.13	10.22
6-12	1737	1665	13.70	1.84	9.64
13-18	1824	1801	13.65	1.88	10.23

Table 3. The distribution of the clinical forms of the lesions in patients with pediatric cutaneous leishmaniasis

n (%)	Nodule	Papule	Ulcer	Recurrent	P
Age (years)					
0-5	463 (45.4)	156 (15.3)	397 (38.9)	4 (0.4)	0.0001
6-12	1617 (47.5)	507 (14.9)	1252 (36.8)	26 (0.8)	
13-18	1698 (46.8)	308 (8.5)	1587 (43.8)	32 (0.9)	
Number of lesions					
1-5	3643 (47.0)	934 (12.0)	3125 (40.3)	56 (0.7)	0.005
6-10	114 (48.3)	30 (12.7)	89 (37.7)	3 (1.3)	
≥11	21 (39.6)	7 (13.2)	22 (41.5)	3 (5.7)	
Duration (weeks)					
1-16	3310 (50.9)	926 (14.2)	2255 (34.7)	8 (0.1)	0.0001
17-32	409 (33.4)	38 (3.1)	764 (62.4)	14 (1.1)	
33-48	30 (21.4)	3 (2.1)	103 (73.6)	4 (2.9)	
≥49	29 (15.8)	4 (2.2)	114 (62.3)	36 (19.7)	
Location of the lesion					
Head/neck	2422 (49.5)	684 (14.0)	1738 (35.5)	53 (1.1)	0.0001
Body	60 (45.1)	15 (11.3)	57 (42.9)	1 (0.8)	
Upper extremities	869 (45.3)	173 (9.0)	871 (45.4)	5 (0.3)	
Lower extremities	374 (37.7)	83 (8.4)	532 (53.7)	2 (0.2)	
Generalized	53 (49.1)	16 (14.8)	38 (35.2)	1 (0.9)	

(52.2%) (16). On the other hand, Aksoy *et al.* found that it was more common among women (53.9%) in a study they conducted with 8786 patients with PCL (8). In our study, the rate of male patients was higher in all three age groups.

Although CL can present at any age, it is more common in childhood (17). The most probable reason for the higher rate among children is exposure to the parasite at early ages and the absence of immunity against the responsible pathogen, in contrast to adults (18,19). Uzun *et al.* investigated 3074 patients with CL and found that 41% of patients were between 10 and 19 years of age (20). In their study, Gürel *et al.* determined that 70% of 2120 patients with CL were under the age of 20 years (21). Aksoy *et al.* conducted a study with patients diagnosed with PCL and reported that the disease was more common in the 6-10 age group compared with the 0-5 and 11-15 age groups (8). In our study, unlike the study of Aksoy *et al.* (8), PCL was more common in adolescents.

As CL can be confused with various skin diseases, misdiagnosis is possible and diagnosis and treatment may thus be delayed. Depending on the delay in diagnosing CL, the diameters and types of the lesions may change (8,14,15). In the study by Aksoy *et al.*, the diameter of the lesions was 12.77 ± 0.11 mm, and the number of lesions was 1.76 ± 0.01 . In addition, the lesions were smaller in the 6-10 age group compared with the 0-5 and 11-15 age groups (8). In our study, similarly to the study by Aksoy *et al.* (8), mean lesion diameter and mean lesion number were determined.

Delays in diagnosis and treatment of CL lead to the atypical appearance of the lesions and affect the duration of the disease. They may also cause undesired permanent wound scars during the healing phase (22). Akçali *et al.* determined that the mean duration of disease was 8.2 ± 6.1 weeks among patients with CL (23). The duration of disease was 8.58 ± 0.21 weeks in the study conducted by Aksoy *et al.* The comparison of patients according to age group showed that the duration of disease was shorter in the 6-10 age group, and the longest duration of disease was in the 0-5 age group (8). In our study, the difference between the groups for the duration of disease was not statistically significant. The longer disease duration in younger children may be caused by exposure to the pathogen being less likely compared with the older children and therefore the absence of immunity development against CL.

CL develops mostly in regions such as the head, neck, arms, wrists, and hands, which are not covered by clothes and can be easily accessed by female sandflies (22). In their study, Akçali *et al.* determined that the face (58.5%), upper extremities and neck (29.8%), and lower extremities (10.7%) were the most common locations of the lesions (23). In the study conducted by Aksoy *et al.*, the authors reported that the lesions were more common in the head/neck and mucosal regions in the 0-5 age group, while the lesions were generalized or located in the lower extremities in the 11-15 age group (8). In our study, the most common site of the lesions was the head/neck, which conforms with the literature data.

The CL lesion usually emerges as an erythematous papule, enlarges gradually within weeks and months, and transforms into a nodule or plaque, which is covered with a firmly-adhered crust in the center (22). In some cases, yellowish-red papulo-nodular lesions may develop around the cicatrix of the primary lesions after months or even years, which are known as the recurrent form of the disease (24). Aksoy *et al.* reported that the most common lesion forms in patients with PCL were ulcerative (57.1%) and nodular (36.6%) lesions. In addition, the rate of recurrent lesions was 2.29% in this study. They also reported that ulcerative lesions were most common in the 11-15 age group, while recurrent lesions were most common in the 0-5 and 11-15 age groups (8). In our study, the most common clinical forms of the disease in patients with PCL were nodular and ulcerative forms, which is consistent with the literature.

The drugs most commonly used in CL treatment are pentavalent antimony (SbV) compounds. These drugs can be administered intralesionally or systemically. In Turkey, the most commonly used method is IL meglumine antimonate (MA) treatment, due to the toxicity risk of the systemic treatment (1,22). However, systemic treatment can be applied if the location, number, size, and form of the lesions are not suitable for IL treatment or if lesions do not respond to the IL treatment (25).

In two studies conducted in Turkey, healing rates were 82.8% and 97% with IL MA treatment (26,27). In the study conducted by Aksoy *et al.*, intralesional antimony treatment was applied more frequently than systemic antimony treatment. The IL antimony treatment was more common in the 6-15 age group compared with the 0-5 age group. It was reported that 66% of the patients in the 0-5 age group received intralesional treatment and healed in one cycle. The authors therefore concluded that the first-line treatment option in the 0-5 age group should be intralesional treatment to avoid the toxic effects of the systemic treatment (8). Based on the existing data, we believe that IL treatment is more suitable as the first-line treatment option in children under the age of 5 years.

In conclusion, our study demonstrated that the intragroup comparison of the age group with the highest CL rate displayed similar clinico-epidemiological characteristics to those reported in the previous studies conducted in the same region. We believe that the findings of our study will contribute to a better understanding of the disease in pediatric patients and to correct decisions on suitable treatment options.

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