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Analysis of associated risk factors among recurrent cutaneous leishmaniasis patients: A cross-sectional study in Khyber Pakhtunkhwa, Pakistan

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ABSTRACT

Background: Leishmaniasis is the second and fourth highest cause of mortality and morbidity respectively among all tropical diseases. Recurrence in the onset of leishmaniasis is a major problem that needs to be addressed to reduce the case fatality rate and ensure timely clinical intervention. Here we are investigating the association of risk factors with recurrent cutaneous leishmaniasis to address this issue.
Material and methods: Patients received by Nasser Ullah Khan Babar Hospital in Peshawar, Pakistan from March 2019 to July 2020 were enrolled in this study. Those patients who developed symptoms after completion of treatment were included in Group-A while those who had atypical scars like leishmaniasis but were negative for cutaneous leishmaniasis were included in the comparison group tagged as Group B. All those individuals who had completed six weeks of treatment for CL but had normal complete blood counts (CBC) were included to avoid other underlying immunological pathologies, while we excluded those participants who had co-morbidities like diabetes, liver disease, cardiac disease, and pregnant and lactating women through their history Association was tested between Group-A and Group-B with other explanatory variables through chi-square test. The regression model was proposed to determine the predictors.
Result: A total of 48 participants of both sexes were included in the study with a mean age of 32.2 ± 15.10. The data suggest that females are overrepresented among the patients with recurrent leishmaniasis [21(53.8 %,); p = 0.07]. Compared to patients; healthy participants had a higher proportion of adults (19–59

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years) versus adolescents (13–18 years) [26(66.7 %) vs 07(17.9), p = 0.004]. Multivariate logistic regression analysis shows that females are 2.1 times more prone to infections among cases as compared to healthy individuals [unadjusted OR 2.20, 95 % confidence interval (CI) 1.5–10.6, p = 0.02; adjusted OR 2.1, 95 % CI 1.50–10.69, p = 0.02]. We propose that patients receiving intradermal were less likely to be infected as compared to those receiving intralesional injections [unadjusted OR 0.07.0, 95 % confidence interval (CI) 1.18–3.37, p = 0.03; adjusted OR 0.06, 95 % CI 1.18–3.38, p = 0.03].

Conclusion: Old age (adults) and sex (females) were the strongest predictors to be associated with recurrent leishmaniasis. Similarly, the choice of intradermal as compared to intralesional injection and the prolonged treatment duration were strongly associated with greater chances of recurrence.

Introduction

Besides being listed as a “neglected disease, Leishmaniasis caused by a protozoan parasite is responsible for the ninth largest disease burden among individual infectious diseases and remains a major global public health problem [1]. According to the World Health Organization, among all tropical diseases, leishmaniasis is ranked as the second highest in mortality and the fourth highest in morbidity worldwide [2], where it contributes to the loss of 2.4 million disability-adjusted life years (DALYs) of individuals [3]. Leishmaniasis is caused by the genus Leishmania which is an obligate intracellular parasite and transmitted by the bite of an infected sandfly by the insertion of promastigotes into humans [4]. There are different clinical forms of Leishmania infection such as visceral leishmaniasis (VL), mucosal leishmaniasis (MCL), and cutaneous leishmaniasis (CL) [5].

The first-line treatment for CL has been based on the intramuscular (IM) administration of meglumine antimoniate (Glucantime)/Sodium stibogluconate both of which are pentavalent antimony (Sb^5) regardless of the number of lesions [6]. However, in 2010 the WHO experts recommend promoting local therapies to encounter uncomplicated CL. Similarly, the use of intralesional injections can also be suggested when systematic treatment is not indicated [7].

Leishmaniasis has been reported in Pakistan in both human and animal reservoirs [8]. It accounts for the second most prevalent vector-borne disease in the country after malaria [9]. Out of total of 70 species reported to date, only 37 are reported to transmit the disease in a healthy host in Pakistan. Areas of interior Sind, Khyber Pakhtunkhwa, and Baluchistan are thought to be endemic areas in Pakistan where Leishmania Tropica is the most predominant species [22] The high prevalence of Leishmaniasis in these areas poses a public health challenge to the government and health professionals [10]. The epidemiology of leishmaniasis is very dynamic and the conditions of transmission are constantly changing in the environment like demography, environment, human behavior, and immunological profile of the affected human population [11]. The control measures are diverse due to the diversity of Leishmania species, biological factors, and reservoir hosts. Besides these, housing, low socioeconomic conditions, and interaction with pets appeared to be associated with increased risk for cutaneous leishmaniasis [12].

Several studies have been carried out over the past few decades to look into possible modifiable and non-modifiable risk factors but to date, no study investigated the relationship of these risk factors with recurrent cutaneous leishmaniasis (RCL). Recurrence is a rare phenomenon where about 5 % of the patients worldwide do not completely heal and the scars reappear after an acute period of the disease. Similarly, a very recent local study highlights the recurrent phenomenon in cutaneous leishmania patients which triggers the immunological and genetic abnormalities [23], so keep in mind the high endemicity and recurrent phenomorphan of CL in this area, the objective of this study was to analyze the associated risk factors among recurrent cutaneous leishmaniasis patients in Khyber Pakhtunkhwa, Pakistan.

Materials and methods

This cross-sectional descriptive study was carried out from March 2019 to July 2020 at Nasser Ullah Khan Babar Hospital in Peshawar, where all the patients suffering from leishmaniasis from the endemic areas of Khyber Pakhtunkhwa, Pakistan are reported for treatment purposes. The study protocol was approved by the ethical committee (1427) of Kohat University of Science and Technology, Kohat while a No Objection Certificate (NOC) was obtained from the administration of Nasser Ullah Khan Babar Hospital, Peshawar. By using the non-probability consecutive sampling technique, both verbal and written informed consent was taken from the study participants or their guardians if the children were less than 10 years of age. A structured questionnaire was adopted and modified from a study conducted by Ngere I et al. [13] where its internal reliability was confirmed by getting 0.80 Cronbach's alpha. Laboratory diagnosis and treatment were given free of charge. They were properly guided about the study objective and were assured of the confidentiality of the data.

Group A included "**Patients with recurrent leishmaniasis**" with infection and dermal scars developing repeated cutaneous leishmaniasis in last one year even after completion of leishmaniasis treatment. The comparison group B, on the other hand, included “**Healthy individuals”** with atypical scars and lesions like CL but without cutaneous leishmaniasis. Initially, the presence of amastigotes in both group A and group B was diagnosed and confirmed through microscopy and then, in the second step, to exclude other pathogens responsible for skin diseases or diabatic ulcers/scars, a genus-specific kDNA and SSU ribosomal PCR were performed which is considered to be the gold standard because of its high diagnostic sensitivity and specificity. These atypical skin lesions and scars were collected by a trained lab technician. Complete treatment was defined as those who received recommended treatment on time. Similarly, healing was defined as the complete restoration of clinical cure scars and their induration after six weeks of treatment. Similarly, healing was defined as the complete restoration of clinical cure scars and their induration after six weeks of treatment. The question of the criteria for completion of treatment was based on past clinical history.

All those individuals who had completed six weeks of treatment for CL but had normal complete blood counts (CBC) were included to avoid other underlying immunological pathologies, while we excluded those participants who had comorbidities like diabetes, liver disease, cardiac disease, and pregnant and lactating women through their history. SPSS version 22 was used for data analysis. continuous variables like age in years, number of injections, and duration of treatments in months. Several lesions present were converted into a categorical variable by dividing the range into three to get a similar

Table 1
Base line characteristics of the participants. Total N = 48.

Categorical variable	Categories	Frequency	Percent
Type of Group	Group A (Recurrent leishmaniasis)	9	18.8
	Group B (Healthy individuals)	39	81.3
Gender	Male	24	50
	Female	24	50
The site of the injection used	Intralesional	29	60.4
	intradermal	19	39.6
Season	March to June	11	22.9
	July to Oct	27	56.3
	Nov to Feb	10	20.8
Which treatment is used	Antibiotic	11	22.9
	Antibiotic&SB5	21	43.8
	SB5	8	16.7
	Local heat&SB5	4	8.3
Which body area?	Face area	13	27.1
	leg area	19	39.6
	Hands	7	14.6
	Mixed parts	9	18.8
Continuous Variable	**Mean**	**SD**	**Minimum -Max**
Age in years	32.25	15.102	09–66
The number of injections	5.79	2.259	02–12
Duration of treatment in months	5.83	1.993	02–11
The number of lesions present	4.79	1.713	02–08

interval of width in each class. The association was tested between group A and group B with other explanatory variables by using the chi-square test. Those variables whose P-value was 0.15 were taken into the regression model to determine the predictors while the multi-regression model was applied to get an adjusted odds ratio for potential confounders. p-value ≤ 0.05 was taken as significant.

Results

A total of 48 participants were included in the study, including Group A and Group B. Mean age of the participants was 32.2 ± 15.1. As Shown in the descriptive statistics of baseline characteristics in Table 1, there was an equal distribution of gender 24 (50 %). Most of the patients were using Antibiotic & SB5 21(43.8 %) and the leg area was the most frequently affected site of the body 19(39.6 %) which was followed by the face 13(27 %).

The data suggest that females are overrepresented among the patients with recurrent leishmaniasis group A [21(53.8 %,); p = 0.07]. Compared to patients; healthy participants (group B) had a higher proportion of adults (19–59 years) versus adolescents (13–18 years) [26(66.7 %) vs 07(17.9), p = 0.004]. Intra lesion was most commonly used as a site of the injection being used [24(61.5 %), p = 0.0] as compared to Intradermal 15(38.5 %) among group A (recurrent Leishmaniasis). More than half cases were documented in July to October season [24(61.5 %): p = 0.06] while the leg area was most commonly observed as a site of infection among group A [16(41.0 %); p = 0.05] Fig. 1. similarly, the most common treatment used among cases were antibiotic & SB5 [16(41.0 %): p = 0.06] while the most frequent treatment duration was 6–9 months among cases [25(64.1 %); p = 0.006]. Details are given in Table 2. Using multivariate logistic regression analysis, females has an odds of 2.1 having recurrent leishmaniasis as compare to healthy individuals [unadjusted OR 2.20, 95 % confidence interval (CI) 1.5–10.6, p = 0.02; adjusted OR 2.1, 95 % CI 1.50–10.69, p = 0.02]. The data shows that as age is directly proportional to the recurrence i.e adults aged > 60 were twice more likely to be affected [unadjusted OR 2.10, 95 % confidence interval (CI) 1.60–2.50, p = 0.002; adjusted OR 2.1, 95 % CI 1.6–02.5, p = 0.002]. Those recurrent leishmaniasis patients who were using

Fig. 1. Patient with recurrent shows scar on the foot.

intradermal as a site of injection compared to Intralesional were less likely to develop recurrence [unadjusted OR 0.07.0, 95 % confidence interval (CI) 1.18–3.37, p = 0.03; adjusted OR 0.06, 95 % CI 1.18–3.38, p = 0.03]. Patients with prolonged treatment duration were more likely to develop recurrence like > 10 months comparing 6–9 months in contrast to healthy individuals [unadjusted OR 02.4, 95 % confidence interval (CI) 0.77–1.87, p = 0.01.2; adjusted OR 3.1, 95 % CI 0.78–1.99, p = 0.01.2]. Details are given in Table 3.

Discussion

Our study demonstrated that most of the patients were using antibiotics and SB5, while the leg area was the most frequently affected site of the body, followed by the face. When comparing recurrent leishmaniasis and healthy individuals, females were more commonly reported with recurrent leishmaniasis, while adults whose ages ranged from 19 to 59 were mostly dominant. Most cases were documented in the July to October season. The most frequent treatment duration was 6–9 months. Our data showed that females were 2.1 times more likely to be infected among cases as compared to healthy individuals. Similarly, as age increases, the cases are likely to be infected, like adults > 60, to get recurrent leishmaniasis. Those cases who were using intradermal injections compared to intralesional were less likely to be infected as compared to healthy individuals. Those whose treatment duration was increasing were more likely to become a case like > 10 months compared to 6–9 months in contrast to healthy individuals. As the number of lesions was increasing in the body, there was a high probability of individuals suffering from recurrent leishmaniasis as compared to healthy individuals [24].

Our results showed that females have a greater chance of being infected with recurrent leishmaniasis. A similar result has also been demonstrated by Mohamed A. Al-Kamel in his study [14]. The reason behind such evidence could be that women suffering from leishmaniasis usually present late to the diagnostic health centres and experience the painful stigma of the disease and physical deformities in local resource-limited environments. In contrast, leishmaniasis is usually reported more frequently among males than females in other regions of the world [15]. This difference could be due to the higher risk of exposure in males, but there are gender-related differences in the host response to infection that may also play a key role. Similarly, increasing age was identified to be a contributing factor but a study conducted by Kayani, B., Sadiq, S., Rashid, H.B., et al. demonstrated age as a proactive factor [16]. They concluded that this correlation might be that children usually go for outdoor activities with minimum precautions, but in our data, the adults who might be more frequently involved in the day-to-day life in our community set up so they have more chance to interact with vectors. The chances of human CL are increased by exposure to the

Table 2
Association of different variables among Recurrent Leishmaniasis and healthy individuals.

Variable	Categories	Type of Group		P Value
		Group B (healthy individuals)	Group A (Recurrent Leishmaniasis)	
Gender	Male	6(66.7 %)	18(46.2 %)	0.07
	Female	3(33.3 %)	21(53.8 %)	
Age	Children (0–12)	0(0.0 %)	4(10.3 %)	0.004*
	Adolescence (13–18)	0(0.0 %)	7(17.9 %)	
	Adult (19–59)	09(100.0 %)	26(66.7 %)	
	Senior adult (> 60)	0(0.0 %)	02(5.1 %)	
Site of the injection used	Intra lesion	5(55.6 %)	24(61.5 %)	0.01
	Intradermal	4(44.4 %)	15(38.5 %)	
Season of treatment	March to June	4(44.4 %)	7(17.9 %)	0.06
	July to October	3(33.3 %)	24(61.5 %)	
	Nov to February	2(22.2 %)	8(20.5 %)	
Site of lesion	Face area	1(11.1 %)	12(30.8 %)	0.05
	Leg area	3(33.3 %)	16(41.0 %)	
	Hands	3(33.3 %)	4(10.3 %)	
	Mixed parts	2(22.2 %)	7(17.9 %)	
Which Treatment used	Antibiotic	2(22.2 %)	9(23.1 %)	0.06*
	Antibiotic&SB5	5(55.6 %)	16(41.0 %)	
	Only Sb5	2(22.2 %)	6(15.4 %)	
	Local heat&SB5	0(0.0 %)	4(10.3 %)	
Number of Injections	02–04	1(11.1 %)	14(35.9 %)	P < 0.05
	05–07	7(77.8 %)	15(38.5 %)	
	> 8	1(11.10 %)	10(25.6 %)	
Treatment duration	2–5 months	6(66.7 %)	12(30.8 %)	0.006*
	6–9 months	3(33.3 %)	25(64.1 %)	
	> 10 months	0(0.0 %)	2(5.1 %)	
Number of lesions	02–04	4(44.4 %)	16(41.0 %)	0.025
	05–06	3(33.3 %)	16(41.0 %)	
	> 7	2(22.2 %)	7(17.9 %)	

Use of Chi Square/*Fisher exact Test.
**P Value ≤ 0.05 as Significant.

body in the open air [17]. The months from May to September are humid and hot in Pakistan, and the people, especially in villages, usually sleep in the open air. The nocturnal activity of the sandflies starts at the beginning of the night and is associated with humidity rather than temperature [18,19]. Our data also supported that the most appropriate transmission period of CL is from July to October, while the part of the body affected was mostly the leg area.

Various therapeutic modalities have been used for CL. Glucuntime (Meglumine antimoniate) remains the first line of treatment for cutaneous leishmaniasis. In this study, patients who were using intradermal as a site of injection compared to intralesional were less likely to be infected as compared to healthy individuals. In contrast, although intralesional therapy for CL treatments has good efficacy, there is weak evidence to support it in

Table 3
Logistic regression analysis by using Recurrent Leishmaniasis and healthy individuals as dependent Variables and its association with other Cofactors.

Independent variable	Categories	Unadjusted OR	95 % CI		P Value	Adjusted OR	95 % CI		P Value
			Lower	Upper			Lower	Upper	
Gender	**Reference value (Male)**								
	Female	2.20	1.5	10.6	0.02	2.1	1.50	10.692	0.02
Age	**Reference value Children(0–12)**								
	Adolescence(13–18)	1.20	1.26	2.3	0.001	01.6	1.26	02.4	0.001
	Adult(19–59)	1.80	1.22	3.6	0.01	01.7	1.22	03.5	0.01
	Senior adult(> 60)	2.10	1.60	2.5	0.002	02.1	1.6	02.5	0.002
Site of injection used	**Reference value (Intralesional)**								
	Intradermal	0.07	1.18	3.37	0.03	0.06	1.181	3.38	0.03
Treatment season	**Reference value (March to June)**								
	July to October	4.57	2.82	25.46	0.05	4.57	2.821	25.46	0.05
	Nov to February	2.28	8.31	16.51	0.04	2.28	8.316	15.12	0.04
Site of Lesion	**Reference value (Face area)**								
	Leg area	0.44	0.04	4.82	1.50	0.44	0.04	5.82	1.50
	Hands	0.11	0.09	1.39	1.27	0.11	0.01	1.50	1.27
	Mixed parts	0.29	0.02	3.83	0.23	0.29	0.02	3.90	0.23
Number of Injection	**Reference value (02–04)**								
	05–07	0.15	0.01	1.40	0.14	0.15	0.01	1.42	0.23
	> 8	0.71	0.04	12.82	0.82	0.71	0.02	10.01	0.15
Treatment duration	**Reference value (2–5 months)**								
	6–9 months	1.16	0.88	19.58	0.34	1.82	0.90	19.53	0.34
	> 10 months	02.4	0.774	1.87	01.2	03.41	0.78	1.99	01.2
Number of lesions	**Reference value (02–04)**								
	05–06	1.33	0.25	6.94	0.10	1.33	0.25	6.94	0.10
	> 7	0.87	0.12	5.94	0.23	0.87	0.12	5.94	0.23

the Americas [20]. A study conducted in Iran showed that there is no association if an injection demonstrated intramuscularly or intralesional [21]. The possible explanation for such a kind of contradiction would be the difference in the genetic profile of the population and also the need for more realistic prospective studies.

This study indicated that in comparison to healthy people, there is a higher likelihood of people developing recurrent leishmaniasis as the number of lesions on the body increases, but in contrast, a study in Iran demonstrated that the number of lesions has no significant association with other explanatory variables like gender [24] Although some literature suggests that the number and size of lesions are correlated with the tumor necrosis factor (TNF), which indicates the dose-response relationship, as the number and size of lesions are increasing, the TNF level is also going to surge [25]. Also, in some other studies, the response to the treatment has a relationship with the number of lesions, which indicates that multiple lesions indicate a poor prognosis [26].

Limitation of the study

The result of this study has some limitations due to its cross-sectional design and small sample size (especially the healthy individuals), as it is difficult to establish the temporal relationship between recurrent leishmaniasis and healthy individuals in such a study design. Moreover, this study design is prone to selection and recall bias. We suggest conducting a cohort study in the future to find out the causal relationship between risk factors and outcomes.

Conclusion

Based on our data, we conclude that old age and female gender were the strong predictors to be associated with recurrent leishmaniasis. Similarly, intradermal injection and prolonged treatment duration are also reported to be associated with a greater chance of getting infected with recurrent Leishmania.

Conflict of interest

None declared.

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