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Cutaneous Leishmaniasis in Iraq: A Continuing Endemic Disease

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Abstract

Background: Cutaneous Leishmaniasis [CL] is still with epidemic and endemic epidemiological characteristics in Iraq.

Aim: To illustrate if there is changes in epidemiological characteristics of Cutaneous Leishmaniasis in Iraq.

Methods: Retrospective descriptive study and data gathered from records in 3 centres in Kirkuk during the period from April, 2015 to end of April, 2016.

Results: The study included 571 cases of clinically diagnosed as CL. The age range of 415 cases was from 1 month to 72 years, with a mean of 21.64 ± 16.95 year. Of the total, 46.58% were female [266/571] and 53.52% were male. The prevalence of CL in Kirkuk city was 67/ 100,000 for clinically diagnosed cases and 18/100,000 for laboratory diagnosed cases.

Conclusion: CL still represents a health care problem with medical and social impact in Iraq. Unavailability of WHO recommendation first - line treatment restricts health care delivery and worsens the problem. The surveillance system and establishment of diagnosis and treatment centres are warranted.

INTRODUCTION

Cutaneous Leishmaniasis [CL] is a skin disease that caused by protozoa of the genus *Leishmania* and humans are infected through the bite of *phlebotomine sandflies* [1]. As there is two types of Cutaneous Leishmaniasis in Iraq, zoonotic [ZCL] and anthroponotic CL [ACL], the disease caused by L. major and L. tropica respectively [2]. In the Eastern Mediterranean Region, ZCL foci reported in Iraq, Jordan, Yemen, Pakistan, Afghanistan, Saudi Arabia, Syria, Egypt, Sudan, Iran, Palestine, Libya, Tunisia and Morocco [3-12], while ACL occurs in Iraq, Yemen, Afghanistan, Iran, Syria, Morocco, Saudi Arabia and Pakistan [13-15].

Epidemiology

In the Middle East and North Africa regions, which included Iraq, there are many neglected tropical diseases [16]. Cutaneous Leishmaniasis with its both clinical forms are widespread in this region [2,11,17-19]. World Health Organization [WHO] considered CL as a major public health problem in the Eastern Mediterranean Region [2] and thus WHO, Eastern Mediterranean Region Organization [EMRO], established strategic plan to address the impact of the problem and perform an effective health care programs for CL infection control. Alvar et al., [20] in their extensive review reported that CL is characterised with more wide distribution than Visceral Leishmaniasis. The global estimates of CL indicated that 70-75% of cases were confined to Iran, Algeria, Afghanistan, Syria, Brazil, Colombia, Ethiopia, Costa Rica, North Sudan, and Peru [20]. For Iraq, the reported cases of CL were 1655/ year for 2004-2008, while the estimated annual CL incidence was 8300 to 16,500, which considered moderate underreporting [20]. CL is endemic in majority of Middle Eastern countries including Iraq, however, the incidence is declining in time in some countries such as Saudi Arabia but continues to spread in others such as Syria and Iraq [21,22].

Figure (1) shows the reported cases of CL in Iraq for 20 years

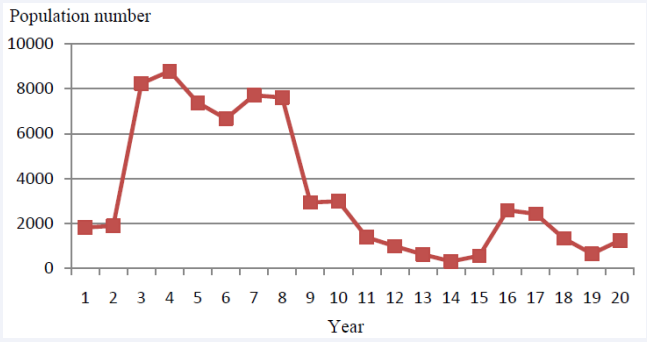

Figure 1 Prevalence of Cutaneous Leishmaniasis in Iraq during the period from 1989-2008.
1 = year 1989; 2 = 1990; 3 = 1991; 4 = 1992; 5 = 1993; 6 = 1994; 7 = 1995; 8 = 1996; 9 = 1997; 10 = 1998; 11 = 1999; 12 = 2000; 13 = 2001; 14 = 2002; 15 = 2003; 16 = 2004; 17 = 2005; 18 = 2006; 19 = 2007 and 20 = 2008

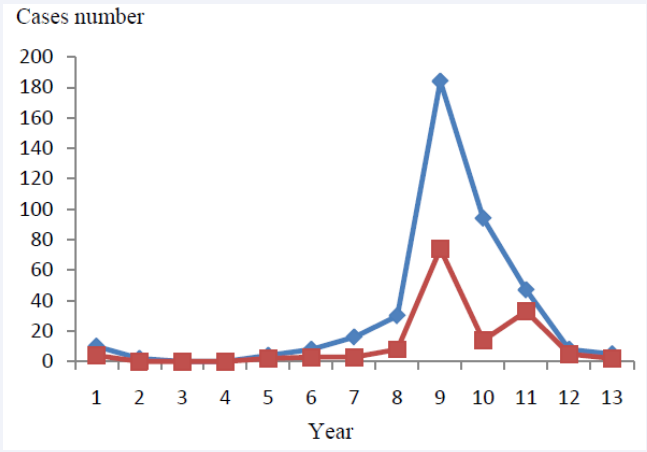

Figure 2 Frequency Distribution of Cutaneous Leishmaniasis for April 2015 to April 2016, Kirkuk.
1 = April 2015; 2 = May 2015; 3 = June 2015; 4 = July 2015; 5 = August 2015; 6 = September 2015; 7 = October 2015; 8 = November 2015; 9 = December 2015; 10 = Jan 2016; 11 = Feb 2016; 12 = March 2016; 13 = April 2016.
Blue line: clinically diagnosed cases.
Red line: laboratory diagnosed cases

period , from 1989 to 2008, the figure illustrated that epidemiology of CL in Iraq is unstable, with large and unpredictable fluctuations in disease incidence and prevalence [18,23] . There are multiple outbreaks that were extended for 6 years from 1991 to 1996; the date for 1st Gulf war indicated the influence of war on disease incidence. Then in 1997, CL incidence declined from 7606 cases in 1996 to 2939 in 1997, with 61.4%reduction, then followed by steady decline to reach 318 cases in 2002, illustrating 96% reduction as compared to 1996 year. In 2003, the trend restart increasing with 17.7% for 2003 as compared to 2002 year, and 81.6% for 2004 and 76.6% for 2005, then decreased by about half and 2/3 of cases for the years 2006 and 2007 respectively. In 2008, CL incidence increased again by 19% as compared to 2007. These information regarding reported cases of CL for 20 years period documented unstable trend of CL prevalence in Iraq.

Iraq faced conflict and political turmoil for long period from 1980 to date, including economic sanction and destruction of infrastructure following American invasion of Iraq. While modernization of the public sector remains a top priority, limited focus on good governance is affecting the implementation of laws, provision of services and effective management of the country's resources. The Iraq Five Year National Development Plan 2010-2014, prepared through a consultative process within governmental and nongovernmental structures, reflects the shift in perspective and approach to development, strengthening a democratic and consultative political base, reforming governance and administration and optimizing the utilization of national natural and human resources [24]. However, most of the plans for recovering and improvement of health care, education, etc. are failed due to extensive managerial and financial corruption and Millennium Development Goals are not achieved.

MATERIALS AND METHODS

In a retrospective study, data gathered from3 health centres in Kirkuk city centre for the period from April, 2015 to end of April, 2016, and included 571 cases of clinically diagnosed as CL. The clinical diagnosis based on lesion characteristics and epidemiological data, while laboratory diagnosis performed using Giemsa stain .The age range of 415 cases was from 1 month to 72 years, with a mean of 21.64 ± 16.95 year. Of the total, 46.58% were female [266/571] and 53.52% were male. Kirkuk city is located 270 kilometres northern to Baghdad and with 851, 000 inhabitants. The prevalence rate determined by dividing number of cases to 851000 and the resulted Figure (1) represent the prevalence per 100000.

Chi square test was used to determine the frequency differences, while student t test was used for mean values comparison. P value of < 0.05 regarded a significant level.

COMMENTS

The higher rate in male as this study indicated was consistent with previously reported studies [22,25-29], but contrasted with others [30-33]. The high incidence of cases in male than female may be attributed to that male are more exposed to sand fly than female [22] due to their outdoor work. There is increase in incidence of CL in female [46.58%] as compared to our previous [43%] study [18] , and this was much lower than the rate in female in a recent study of Hassan et al. [32], [61.6%] in Kirkuk governorate than this study [46.58%]. The prevalence of CL in Kirkuk city was 67/ 100,000 for clinically diagnosed cases and 18/100,000 for laboratory diagnosed cases (Table 1). Thus, the prevalence of clinically diagnosed cases was higher to that reported in a Haweja, Kirkuk, for October 2004 to April 2005 [18]. However, laboratory diagnosed cases incidence in this study was 18/100,000, while that in previous study for Haweja was 33/100,000. This difference in CL incidence may be due to that Haweja community was semi - urban and mixed urban and rural population. In addition, the low incidence in Kirkuk city may reflect the actual epidemiology of cases in urban population and this low incidence was consistent with that reported recently for Kirkuk [32]. The present study prevalence was higher to that reported in Samara (1994), Tikrit (2000), and Kirkuk (2000) in Iraq [33-37] and Afghanistan, Eastern Venezuela, Iran, Saudi

Table 1: Cutaneous Leishmaniasis cases in Kirkuk city.

Centre	Clinically diagnosed cases	Laboratory diagnosed cases [%]
A	184	82 [44.57]
B	231	72 [31.17]
C	156	0.0 [00.00]
Total	571	154 [26.97]
37.11% if centre C excluded.		

Arabia, Tunisia, and Turkey, [3,30,38,39], but lower to that reported for Syria in 2012 [21]. The prevalence of laboratory diagnosed cases was 18/100,000 and this about similar to that reported recently [17/100,000] for Kirkuk [32].

The new cases of CL tended to increase in October and November 2015 and reach peak incidence in December (Figure 2), and subsequently decline in January 2016 and February 2016. This trend of cases peak about two months earlier to our previous report concerning Haweja, as the peak was in January and February. This finding not consistent with that reported by Al - Obaidi [25], and Hassan & Ahmed [32], as their studies population included mixed samples from rural and urban communities. This difference in seasonal variation in cases peak could be attributed to that the study population in the previous study was from rural area while the present study population mainly from urban area. Seasonal variation peak reported in different studies may be due differences in dominant reservoir species in the study site. The differences in seasonal and/or regional variation in incidence could be due to variation in distribution and bionomic of sand flies [40]. Climate changes and seasonal variations are with effect on the distribution of CL vectors and subsequently affect the disease epidemicity and endemicity [41].

Figure (2) shows disparity between clinical and laboratory diagnosis, laboratory diagnosis was confirmed in 26.97% of cases and thus 73.13% of the clinically diagnosed cases are not confirmed in Giemsa stain. This indicated low sensitivity of the Giemsa stain and high specificity and this contrasted with our previous report [18]. The clinical diagnosis of the CL cases presented in this study was performed by 12 dermatologists which indicated that misdiagnosis is unlikelihood. Based on epidemiological data and clinical features, Cutaneous Leishmaniasis may be accurately diagnosed in majority of cases. Thus this low sensitivity of the Giemsa stain may be due to improper sampling or slide preparation or Giemsa stain storage and this confirmed by that all clinically diagnosed cases were negative in laboratory test. Giemsa stain was with high sensitivity [93%] in our previous study [18] and that reported by other [32]. However, previous studies reported a low sensitivity of direct examination test (50-70%), culture (44-58%), and animal inoculation (38-52%) [42-44]. Hassan and Ahmed [32] reported sensitivity of 63.6% for direct microscopy, 83.5% for culture and 94.5% for ELISA serological test.

Immunohistochemistry detect *Leishmania* antigen in 88.5% of cases and *Leishmania* amastigotes in 41.4% of cases [45]. Although, other serological tests such as immunofluorescence and ELISA are commonly used test for the diagnosis of CL, however, are with low sensitivity and specificity [42,46-49]. Homogenous species antigens in direct agglutination tests increased its sensitivity and specificity [42,50], however, presence of different species in the same area may affect its result outcome and low antibody titre in CL may influence the sensitivity of the test [42] Nowadays, the new trend in diagnosis of infectious diseases is the molecular technique, polymerase chain reaction, and reported studies indicated its high specificity [51-58] and to differentiate between different *Leishmania* strains [32]. Alsalem [59] recently developed a diagnostic tool for CL by ELISA to measure serum anti-α-galactosyl antibodies using synthetic neoglycoproteins, with a sensitivity of 91% for *Leishmania tropical* and 96% for *Leishmania major.* There are significant differences in rate of laboratory diagnosis between centres [X^2 =7.88; P= 0.006], low laboratory diagnosis in centre C, 31.2% in centre B, and 44.6% in centre A, Table (2). Laboratory diagnosis not show significant gender differences [X^2 = 0.054, P > 0.05] (Table 3).

The high laboratory diagnosed CL rate was 18.8% in subject with age of ≤ 5 years, while the lower diagnosis rate was 3.9% in age group of 31-35 years (Table 4). In addition, 47.3% of the CL cases are with age of ≤ 15 years and this rate was higher that reported for Haweja (2004-2005) [43%], but the difference was not significant. Thus the frequency of cases was 52.7% in subjects older than 15 years and this rate was lower to that reported Colombia (86%) [60], but lower to that reported for Kirkuk, Iraq (15.1%) [32], Iran (38%) [28] and Turkey (45%) [30], Baghdad, Iraq (76%) [33], Wasit, Iraq [29]. There is no significant difference in mean age between laboratory CL positive and negative cases (Table 5).

Although CL is considered a self - limiting disease, however, drug used to reduce the lesion scar formation [22]. The treatment outcomes influenced by parasite factor, host response factor and drugs characteristics such as pharmacodynamics and pharmacokinetics. The drugs used for treatment of CL form a long list in literature, however, it is difficult to drain conclusion regarding the most effective treatment approach [42,61-77]. Challenges for development of effective therapy for CL still present and thus screening for effective drugs in an appropriate models and standardized clinical trials are warranted [78].

In animal model, we evaluated the efficacy of 3 drugs for

Table 2: Laboratory diagnosis according to centres.

Centre		Laboratory Diagnosis		Total
		Negative	Positive	
A	Count	102	82	184
	% within Centre	55.4%	44.6%	100.0%
	% within Lab Diagnosis	39.1%	53.2%	44.3%
B	Count	159	72	231
	% within Centre	68.8%	31.2%	100.0%
	% within Lab Diagnosis	60.9%	46.8%	55.7%
C	Count	156	0	156
	% within Centre	100.0%	0.00%	100.0%
	% within Lab Diagnosis	100.0%	0.00%	100.0%
X^2 =7.88; P= 0.006				

Table 3: Laboratory diagnosis in relation to gender.

Gender		Laboratory Diagnosis		Total
		Negative	Positive	
Male	Count	141	85	226
	% within Gender	62.4%	37.6%	100.0%
	% within Lab Diagnosis	54.0%	55.2%	54.5%
	% of Total	34.0%	20.5%	54.5%
Female	Count	120	69	189
	% within Gender	63.5%	36.5%	100.0%
	% within Lab Diagnosis	46.0%	44.8%	45.5%
	% of Total	28.9%	16.6%	45.5%
Total	Count	261	154	415
	% within Gender	62.9%	37.1%	100.0%
	% within Lab Diagnosis	100.0%	100.0%	100.0%
	% of Total	62.9%	37.1%	100.0%
X^2= 0.054, P > 0.05				

Table 4: Laboratory diagnosis according to age groups.

Age group		Laboratory Diagnosis		Total
		Negative	Positive	
<1-5	Count	51	29	80
	% within Age group	63.7%	36.2%	100.0%
	% within Lab Diagnosis	19.5%	18.8%	19.3%
	% of Total	12.3%	7.0%	19.3%
6-10	Count	37	25	62
	% within Age group	59.7%	40.3%	100.0%
	% within Lab Diagnosis	14.2%	16.2%	14.9%
	% of Total	8.9%	6.0%	14.9%
11-15	Count	31	19	50
	% within Age group	62.0%	38.0%	100.0%
	% within Lab Diagnosis	11.9%	12.3%	12.0%
	% of Total	7.5%	4.6%	12.0%
16-20	Count	22	16	38
	% within Age group	57.9%	42.1%	100.0%
	% within Lab Diagnosis	8.4%	10.4%	9.2%
	% of Total	5.3%	3.9%	9.2%
21-25	Count	19	12	31
	% within Age group	61.3%	38.7%	100.0%
	% within Lab Diagnosis	7.3%	7.8%	7.5%
	% of Total	4.6%	2.9%	7.5%
26-30	Count	27	20	47
	% within Age group	57.4%	42.6%	100.0%
	% within Lab Diagnosis	10.3%	13.0%	11.3%
	% of Total	6.5%	4.8%	11.3%
31-35	Count	16	6	22
	% within Age group	72.7%	27.3%	100.0%
	% within Lab Diagnosis	6.1%	3.9%	5.3%
	% of Total	3.9%	1.4%	5.3%
36-40	Count	14	7	21
	% within Age group	66.7%	33.3%	100.0%
	% within Lab Diagnosis	5.4%	4.5%	5.1%
	% of Total	3.4%	1.7%	5.1%
41-45	Count	13	7	20
	% within Age group	65.0%	35.0%	100.0%
	% within Lab Diagnosis	5.0%	4.5%	4.8%
	% of Total	3.1%	1.7%	4.8%
≥ 46	Count	31	13	44
	% within Age group	70.5%	29.5%	100.0%
	% within Lab Diagnosis	11.9%	8.4%	10.6%
	% of Total	7.5%	3.1%	10.6%
Total	Count	261	154	415
	% within Age group	62.9%	37.1%	100.0%
	% within Lab Diagnosis	100.0%	100.0%	100.0%
	% of Total	62.9%	37.1%	100.0%
X^2=3.47; P > 0.05				

Table 5: Mean age in relation to laboratory diagnosis.

Laboratory Diagnosis	N	Mean age In year	Std. Deviation	Std. Error Mean
Negative	261	22.2	17.0	1.05
Positive	154	20.8	16.9	1.35
t=0.82; P > 0.05				

treatment of CL; the cure rate was 100% for ivermectin, while it was 70% for pentostam, 60% for berenil, 50% for amphotericin B, and 50% for metronidazole [79]. Liposomal amphotericin B induced a cure rate of 84% for Cutaneous Leishmaniasis caused by 5 different *Leishmania* strains [80]. In addition, Oliveira et al. [81], developed fluconazole - loaded micro emulsions demonstrated leishmanicidal activity and thus micro emulsions are a promising drug delivery system in CL. The derivatives of 2-nitrovinylfuran have a potential anti Leishmanial activity *in vitro* and *in vivo* [82].

Khraiwesh et al., [83] found that 14 from 400 screened compounds from Medicine for Malaria Venture with anti Leishmanial activity, which may be used for development of Cutaneous Leishmaniasis drugs. Local heat therapy shows cure rate for CL due to Leishmanial major similar to intravenous sodium stibogluconate with less toxicity [84].

The first line drug for treatment, pentavalent antimonilial drugs [meglumine antimoniate and sodium stibogluconate] as recommended by WHO are not available for every CL case. In addition, amphotericin B and pentamidine are not available and thus the drug unavailability attribute to health and social impact due to cosmotic side effect of scar formation. Although, there are many alternative drugs for CL treatment, rifampicin is the mostly used as alternative treatment because it is available even on counter. Our team used liquid nitrogen cryotherapy as the first line treatment for CL, especially in children without the side effect of local, multiple, and repeated injections. This approach results consistent with the findings of others [85]. Our alternative for cryotherapy is rifampicin or azithromycin.

Although, effort performed globally for development of effective drugs for the treatment of Cutaneous Leishmaniasis which represent a social disease in our community due to disfigurement induced by lesion. However, still there is a gap in the treatment of CL and lack of using standardized protocol to evaluate anti Leishmanial activity hamper and challenge drug development [86].

The treatment and control of CL in Iraq facing threats and challenges such as population movement, overcrowding, lack of safe water and hygiene, and poor access to health services [1,24].

CONCLUSION

CL is still represents a health care problem with medical and social impact in Iraq. Unavailability of WHO recommendation first - line treatment restricts health care delivery and worsens the problem. The surveillance system and establishment of diagnosis and treatment centres are warranted.

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