Spatial modeling of cutaneous leishmaniasis in Iran from 1983 to 2013

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A B S T R A C T

Introduction: Cutaneous Leishmaniasis (CL), a parasitic skin infection caused by Leishmania species, is endemic in some regions of Iran. In this study, the effect of location on the incidence and distribution of CL in Iran was studied.

Methods: We collected data including the number of Cutaneous Leishmaniasis cases and populations at-risk of disease in Iran’s different provinces reported by the Iranian ministry of health and the National Bureau of Statistics, respectively. Spatial modeling was performed using ArcGIS software. Descriptive maps, hotspot analysis, and high/low clustering analysis were used to demonstrate distribution of the cutaneous leishmaniasis, to determine regions at risk of disease’s incidence, and to reach the most appropriate method for clustering of disease.

Results: The total number of cases of cutaneous leishmaniasis reported through the study period was 589,913. The annual incidence of CL was estimated to be 30.9 per 100,000 in Iranian population. We also demonstrated that Cutaneous leishmaniasis most prominently occurs in regions with dry and desert climates as well as in central parts of Iran. It affected the southwest of Iran between 1983 and 1997, and subsequently developed towards the center and the eastern between 1998 and 2013. Disease hotspots were focused in the provinces of Yazd, Khozestan and Kohgiluyeh-Boyer-Ahmad (p < 0.05). No pattern of spatial clustering was observed.

Conclusion: Cutaneous leishmaniasis is a major health problem which could be a serious threat for inhabitants who live in high-risk provinces of Iran; much more resources need to be allocated in these areas, to warrant the prevention as well as effectively management of this disease.

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1. Introduction

Cutaneous leishmaniasis (Akhvediani et al., 2010), a parasitic skin infection caused by a range of Leishmania species, is a public health problem affecting more than 60 countries located in tropical and subtropical regions worldwide (Desjeux, 2004). The total number of people affected is estimated to be 12 million. Between 2010 and 2015, 1 million newly infected cases of CL were reported (Leishmaniasis and facts, 2014; Shirzadi, 2012). In addition, approximately 90% of cases have been reported from Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia and Syria (Mirzazadeh et al., 2009). Victims infected often have lesions on their skin, without developing any other symptom (Anon, 2014a).

Being bitten by sandflies is the most common route of transmission for Leishmania. Both types of CL have been reported in Iran, including anthropoponotic cutaneous leishmaniasis, or ACL caused by Leishmania tropica and transmitted by Phlebotomus sergenti, and zoonotic cutaneous lieshmaniasis, or ZCL caused by Leishmania major and transmitted by Phlebotomus papatasi (Mohebali et al., 2004; Nadin et al., 2008).

CL is distributed unevenly among the provinces of Iran (Salahimoghadam et al., 2015) and has imposed a significant adverse effect on the health system, as in 2008 alone, over 26,000 cases with an incidence of 37 per 100,000 were reported (Shirzadi, 2012; Akhoudi et al., 2013). There been various cities in Iran wherein CL has been developed, including: Bam (Mohebali, 2013; Chelbi et al., 2009), Mobarakhe, Natanz, Kashan, Ardestan (Gage et al., 2008; Kawa and Sabroza, 2002), Mehran and Dehloran (Raymond et al., 2003). Some studies have also introduced different carriers for leishmaniasis in Iran such as: Ph. papatasi, Ph. major, Ph. alexandri,
There are also a couple of studies showing that some reservoirs of cutaneous leishmaniasis such as *R. opimus* and *M. libycus* are found more frequently in areas with high incidence of the CL like: Mobarakeh, Natanz, Kashan and Ardestan in Isfahan province, Ardakan in Yazd province and Marvdasht and Niriz in Fars province (Mohebali et al., 2004; Nadim et al., 2008). Because of being vector borne and the fact that ZCL variant has non-human sources, certain weather conditions such as specific temperature, humidity and rain, are crucial factors in developing transmission (Mohebali, 2013). Moreover, some researches have declared that CL more frequently occurs in dry areas such as deserts (Chelbi et al., 2009; Gage et al., 2008).

Considering these circumstances, geographical factors, especially location, play a significant role in the incidence of CL both in human and animals. This effect has been evaluated using a Geographic Information System (Schröder, 2006). This system is capable of determining high-risk areas or “hotspots”, as well as any non-random accumulation, or “clustering” of the disease. Additionally, several studies have utilized the GIS system to assess the distribution of leishmaniasis (Franke et al., 2002; Kawa and Sabroza, 2002; Raymond et al., 2003; Salomon et al., 2004). A study conducted in 2014 indicated a higher incidence in the rural plateaus of Iran (Salahi-Moghaddam et al., 2015). Similarly, there are couples of investigations on distribution of the CL in certain places such as deserts, plains, low-altitude, and high-density areas that have revealed the presence of a clustering pattern (Chelbi et al., 2009; Salomon et al., 2004; Balmaa et al., 1994; Ben-Ahmed et al., 2009; Demirel and Erdoğan, 2009; Rodríguez et al., 2013; Salah et al., 2007).

Given the extent of different foci and the geographical distribution in Iran, identification and examination of high-risk foci of CL and their time trends can be used as an effective tool to improve health services’ quality. In addition, GIS has been efficiently served to accomplish this goal. To our knowledge, the distribution of CL (ACL and ZCL) by using GIS analysis has not yet thoroughly been studied in Iran. In this study, we examined reported data of CL incidence in Iran (between 1983 and 2013) and used a spatial model to identify high risk areas and also to look for evidence of disease clustering. The results will shed the lights for stakeholders to appropriately allocate resources targeting disease management and prevention in Iran.

2. Methods

2.1. The study area

Iran, a country in the Middle-East with the extent of 1,648,195 square-kilometers, has been ranked as the 18th largest country in the world with a population of over 75 million (2011) (Pappas et al., 2006). It has possessed a variety of environmental features such as a vast geographical length and breadth, topographic diversity, and an altitude up to 5671 m above sea level. The Iran’s climate ranges from arid to subtropical, and the mean of rainfall varies from 100 to 2000 mm with a temperature ranging from 0 to 50 °C. Being surrounded by Armenia, Turkmenistan, and Azerbaijan at the north, (as well as by Russia and Kazakhstan via a water border in the Caspian Sea); Afghanistan and Pakistan at the East; the Persian Gulf and Gulf of Oman at the south; Iraq at the east; and Turkey at the northwest (Mostafavi et al., 2013), Iran has been currently divided into 31 provinces.

2.2. Reported incidence of CL

Reported data about the incidence of cutaneous leishmaniasis from the beginning of 1983 until the end of 2013 was collected at a provincial level. After cleaning and correcting of errors, information were entered into Excel datasheets. In situations where the only information was the number of cases reported, the incidence was calculated (Eq. (1)) by the extraction of populations at risk (total population of the province), reported by the National Bureau of Statistics.

\[
\text{Incidence} = \frac{\text{Number of reported cases}}{\text{Total Population Risk}} \times 100,000
\]

Eq. (1): Incidence of cutaneous leishmaniasis.

2.3. GIS analysis

The most recently updated electronic map of Iran and its provinces was used and linked this map to excel file by join comment.

A choropleth map that uses a range of colors to show variable changes in the layers of polygons produced at the provincial level. A choropleth map of CL in time frames of 1, 5, 10, 15 and 31 years was created, for the reason of better detecting likely changes of distribution of CL.

Disease hotspots were identified by using the Getis-Ord Gi* statistic. The Hot Spot Analysis tool calculates the Getis-Ord Gi* statistic (Eq. (2)) for each province in a dataset. The resultant Gi score tells us how provinces with either high or low incidences spatially cluster. This tool works by analyzing each province within the context of neighboring provinces. A province with a high incidence of CL was considered to be a statistically significant Hot Spot especially when being surrounded by provinces with a high incidence. The value belonged to a particular province was compared proportionally to that of the rest provinces; if the local value is much different than the expected local sum and difference is too large to be the result of random chance, a statistically significant Gi score would be obtained. To the contrary, a cold spot province is the one in which a low Incidence of CL is detected and also is surrounded by provinces with low Incidence (Anon, 2014b; Mahbubeh et al., 2014; Asgari, 2011).

\[
G_i = \frac{\sum_{j=1}^{n} w_{ij} \cdot X_j - \bar{X} \sum_{j=1}^{n} w_{ij}}{S} \]

Eq. (2): Getis-Ord Gi* (Gi* Statistics) – where Xj is the Incidence of CL for province j, wij is the spatial weight between province i and j, n is equal to the total number of provinces.

\[
G = \sum_{i=1}^{N} \sum_{j=1}^{N} w_{ij} \cdot X_i \cdot X_j \]

\[
S = \sum_{i=1}^{N} \sum_{j=1}^{N} w_{ij} \]

Eq. (3): G statistics where Xi and Xj, respectively, are the Incidence of CL in the i-th and j-th Provinces; Wi is the spatial weight between the Province i and j; N is the total Incidence of CL; and S0 is the aggregate of all spatial weights.

For hot-spot analysis, spatial weight calculated by Fixed Distance Band method. In this method, each province is analyzed within the context of neighboring provinces. Neighboring provinces inside the specified critical distance receive a weight of one and exert influence on computations for the target province. Neighboring provinces outside the critical distance receive a weight
of zero and have no influence on a target province’s computations. Also for determine of critical distance we used Euclidean Distance method that is straight distance between two polygons center. In other word, it is minimum distance between two polygons center. Center of polygons determines by centroid method. For weighting, we don’t use standardization.

High/Low Clustering analysis was also used for detecting the concentration of high or low incidence of CL for the chosen study area. To achieve this goal, we used General statistics (G statistics), a method developed by Getis and Ord capable of measuring how the high or low incidence areas are distributed (Mollalo et al., 2015). A positive or negative z-score for G(d) indicates spatial clustering of high or low incidence, respectively (Eq. (3)) (Asgari, 2011).

3. Results

The total number of reported cases of CL (based on clinical characteristics and pathologic positive findings) during the study period (1983–2013) was 589,913. Nationally, the average annual reported incidence was estimated to be 30.9 per hundred thousand people. There was a primary increasing and a secondary sharp decreasing trend over these years. The lowest reported incidence of CL was seen in 1992, increased in 1997, and then significantly declined until 2001. The reported incidence of the CL rose again between 2001–2003, which represented a gradually raised rate until the end of the study (2013) (Fig. 1).

It should be noted that the highest incidence of the CL was seen in the provinces of Isfahan, Fars, Boshehr, Ilam, Khozestan, Yazd, Semnan, Kerman and Khorasan, whereas the low-incidence ones were Gilan, Kurdistan, Azerbaijan-West, Ardabil, Tehran, Qazvin, Hamadan, East-Azerbaijan, Kermanshah, Kohgiloyeh-Boyer-Ahmadi, Lorestan, Markazi and Chaharmahal-Bakhtiari (Fig. 2).

Based on first fifteen years map, Isfahan had the highest rate of incidence between 1983 and 1997, and Khozestan and Boshehr were ranked next. Ilam, Kerman and Fars developed modest value of incidence, compared to other provinces. The remaining provinces reported lower incidence. However, in second fifteen years map, particularly between 1998 and 2013, the most cases of cutaneous leishmaniasis were reported from Ilam, Fars and Yazd when compared to the rest of provinces. Additionally, Kerman, Isfahan, Khorasan-razavi and Semnan ranked next (Figs. 3 and 4).

Most cases of cutaneous leishmaniasis at the end of period in this study was reported from Ilam. Interestingly, compared to 1983–1997, the pattern of incidence reported between 1998 and 2013 shifted to the central and north-eastern provinces, indicating that provinces with a higher rate of infection in the beginning of study showed thereafter lower cases.
4. Hot spot and cold spot analysis

4.1. Hot spots

The result of Getis-Ord Gi* statistic that was used to detect Hot Spot areas through the first fifteen years Hot-Spot map uncovered that in 1983–1997, Kohgiluyeh-Boyer-Ahmad Province (p < 0.01) and Yazd and Khuzestan Provinces (0.05 > p > 0.01) were classified as significant Hot Spot areas of cutaneous leishmaniasis. However, Chaharmahal-Bakhtiari and Bushehr Provinces, although not statistically significant, classified as Hot Spots (Fig. 5). In addition, Hot-Spot map related to the second fifteen years classified Yazd Province (0.05 > p > 0.01) as an obvious Hot Spot area. Although Khorasan-South classified as Hot Spots but it was not significant at level 0.05 (Fig. 6). Hot Spot analysis in a period of fifteen-year has demonstrated a tendency of cutaneous leishmaniasis Hot Spots to progress from southwest towards the center and east of the country.

4.2. Cold-spots

Based on first fifteen years Hot-Spot map, Ardabil, East-Azerbaijan, West-Azerbaijan, Kermanshah (0.05 > p > 0.01) Kurdistan, Zanjan, Qazvin and Gilan (p < 0.01) were classified as significant Cold-Spots of CL. However Hamedan province, although not statistically significant, classified as Cold-Spot of CL (Fig. 5). Based on second fifteen years Hot-Spot map, the provinces of Ardabil, Azerbaijan-East, Azerbaijan-West, Hamedan, Kurdestan...
(0.05 > p > 0.01). Zanjjan, Qazvin and Gilan (p < 0.01) were also included in this order. Resemble to Hamedan, Markazi and Qom provinces classified Cold-Spots of CL despite of not statistically significance at the level of 0.05 (Fig. 5). Provinces of the northern and northwestern provinces were at lower risk and detected as Cold-Spots.

4.3. High/low clustering analysis

The analysis of high/low clustering conducted in the beginning fifteen years, implies that datas are normally distributed, although no tendency towards high or low frequencies was observed.

5. Discussion

The total number of 589,913 cases of cutaneous leishmaniasis was reported during the time of this study (1983–2013). Since the number of undiagnosed cases, regarding the available literatures, is estimated to be 3 to 5 times higher (Shirzadi, 2012; Anon, 2014a), approximately 3 million people were infected during this period of time. The timeline graph of incidence in 31 years showed that the rise and fall in CL incidence does show a cyclical pattern, with each period lasting 4–5 years. Nevertheless, the incidence had been declined dramatically by the end of the study and no periodic trend was observed.

Other investigations have reported that this periodic trend takes 5–6 years (Salah et al., 2007). This may be due to changes in the population of wild rodents (as a reservoir of cutaneous leishmaniasis) and human intervention, dispersion of vectors, changes in climate and people’s lives and the lack of relative immunity in populations living in areas where the disease is prevalent (Nadim et al., 2008).

We indicated that distribution of the CL in Iran has a particular pattern, as cold areas, such as northern and northwestern provinces, mainly located along the Zagros and Alborz Mountains represent a lower incidence of CL. Because of the high altitude of these areas; the common CL carriers cannot transmit the pathogen at high altitudes. Several studies have shown an inverse relationship between the altitude and incidence, as altitude increases, incidence of CL decreases (Salahi-Moghadam et al., 2015; Ali-Akbarpour et al., 2012). Because of being cold, which influences the survival of vectors and parasites, these areas show a lower rate of infection. In other words, there is an inverse relationship between cold weather and cutaneous leishmaniasis occurrence (Nadim et al., 2008; Ali-Akbarpour et al., 2012). Therefore, it appears to exists in desert areas far away from the central highlands of the country (Zagros and Alborz Mountains) (Salahi-Moghadam et al., 2013).

The results of this study showed a more CL prevalence in the central and plains provinces, where the geographical condition facilitates the survival and propagation of the reservoirs and carriers. *P. papatasi*, as the rural carriers of cutaneous leishmaniasis, is found profoundly in Iran’s plains (Nadim et al., 2008). In addition, carriers in Isfahan, Lofatabad (Khorasan-razavi), Turkmen Sahra (Golestan), Ahvaz, Dezful and southern Sistan va Baluchistan were found abundantly, making them areas with a high rate of infection (Nadim and Faghih, 1968; Nadim et al., 1968). Similarly, other studies have demonstrated that arid areas and deserts, because of having an ideal humidity and temperature, are thought to be important sources of carrier, *Ph. Papatasi*. (Chelbi et al., 2009; Singh, 1999). There are also studies showing that reservoirs of cutaneous leishmaniasis such as *R. opimus* and *M. libycus* are found more frequently in areas with high incidence of the cutaneous leishmaniasis (Nadim et al., 2008). However, later in the study, the reported incidence of the CL in Iran declined and the highest incidence belonged to Ilam Province, which has been ranked highest since 2010.

During the study period in total, Isfahan, Fars, Booshehr, Ilam, Kohzestan, Yazd, Semnan, Kerman and Khorasan were included as areas with high incidence. Conversely, lower burden of infection was reported from Gilan, Kurdestan, Azerbaijan-West, Ardabil, Tehran, Qazvin, Hamedan, Azarbaijan-East, Kermanshah, Kohgiluyeh-Boyer-Ahmad, Lorestan, Markazi and Chaharmahal-Bakhtiari. Other studies have shown resemble results (Salahi-Moghadam et al., 2015; Karimi et al., 2014). Increased incidence of the CL in the provinces mentioned above has to do with the likely infection sources, such as: (Seyedi-Rashiti et al., 1983; Sharifi et al., 1998), Mobarakeh and Borkhar, Natanz, Kashan and Ardestan in Isfahan, (Parvizi et al., 2010; Talari et al., 2006; Yaghoubi-Ershadi et al., 1999, 1995) and the cities Mehran and Dehloran in Ilam (Kassiri et al., 2012).

Fifteen years – descriptive maps showed an incremental CL incidence in provinces like Ilam, Fars and most of centrally located areas later in the study; whereas high-incidence provinces in had primarily shown a lower incidence. The frequency of disease in the beginning of the study was found to be higher in the west, such as in Kohzestan and Booshehr, and then gradually moved towards the center, south, and northeast of the country.

Analysis of cutaneous leishmaniasis hotspots for the reason of determining the most important sources of the study has been widely used (Salah et al., 2007; Mahbubeh et al., 2014; Kassiri et al., 2012). The provinces of Yazd and Kohgiluyeh-Boyer-Ahmad were finally identified as potential foci throughout this investigation.

Other studies have also demonstrated the high incidence of cutaneous leishmaniasis in Yazd Province, but ranked Kohgiluyeh-Boyer-Ahmad as having a low incidence. This can be explained by being neighborhood with provinces with high-incidence, such as: Kohzestan, Booshehr, Fars and Isfahan, resulting in a significant spatial weight in the hotspot analysis (Seyedi-Rashiti et al., 1983; Sharifi et al., 1998; Parvizi et al., 2010; Talari et al., 2006; Yaghoubi-Ershadi et al., 1999, 1995). Another explanation has to do with undiagnosed cases attributed to lack of either resources or infrastructure found in neighboring provinces. On the other hand, provinces in the north-east have always been known as coldspots with the incidence less than the national average.

In addition, hotspot analysis in fifteen-year periods has demonstrated a tendency of infection hotspots to move towards the center and the east of the country. This may reflect the administered control measurings in high-risk areas. is the geographical condition appears to be an important contributory factor, although being influenced by a variety of factors including latitude and longitude, temperature, humidity, and soil as well as control programs and training.

Using the GIS system, we attempted to demonstrate any impact of location on the incidence of CL as well as possible shifts of hotspots or foci. Based on the results of this study indicate declining rate of incidence in old foci with the emergence of new ones. Moreover, the CL foci shifted towards the center and east of the country. Some studies have shown that a cycle of leishmaniasis infection may take place in certain locations. A study by Demirel et al. in Turkey revealed that the CL incidence is higher in the southeastern regions (Demirel and Erdoğan, 2009).

Several studies have suggested a cluster pattern in time and location for cutaneous leishmaniasis incidence. In an attempt to identify the clustering of cutaneous leishmaniasis in certain pre-specified timeframes, Salah et al. showed more clusters close to hydroelectric dams (Salah et al., 2007). Chelbi et al. also found the clusters of the CL in dry and desert areas (Chelbi et al., 2009). Clustering of the CL was reported by other studies (Barbosa et al., 2014; Elnaiem et al., 2003; Sudhakar et al., 2006) as well. However, no cluster was identified in this study. Other studies have reported different results in terms of segments analyzed, which were small, hence the polygons (number of regions) increased, making it more


different types of leishmaniasis. In addition, since the information had been gathered at the provincial level, the precision of spatial analysis might be decreased Accordingly, collecting the information of the CL infection separately for urban and rural areas is recommended in future surveillance systems.

Regarding our findings, cutaneous leishmaniasis is found to be a public health problem Iran, where planning to control and taking appropriate measures to reduce the incidence are urgently needed. Appropriate control measuring programs such as health education through public media as well as individual and group training; reduction of animal reservoirs; case-finding and timely treatment, especially in urban Cutaneous leishmaniasis; modification of favorable environments and proper disposal of waste; sterilization of carriers; and the immunization of people at risk, through leishmanization with Leishmania major produced using standard methods, is proposed to be exerted (Shirzadi, 2012; Nadim et al., 2008).

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