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The Prevalence of Leishmaniasis in Pakistan: A Review

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Review Article

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Abstract: This review is about the most prevalent disease Leishmaniasis at the various areas of Pakistan. This paper explains Leishmania as the cause of the disease, geographical distribution of its species, genome, morphology, vector specie, clinical forms, treatment, control and epidemiology of the Leishmania at various provinces and cities of Pakistan and its neighboring countries. The paper briefly concludes the main source of the prevalence of the disease and the precautionary measures that should be taken against Leishmaniasis.

Keywords: Leishmania, genome, morphology, vector specie, clinical forms, treatment, control, and epidemiology.

INTRODUTION

Leishmaniasis a deserted disease in the tropical regions of the world, mainly caused by Leishmaniasis (protozoan parasite found intracellularly) belongs to the family of Trypanosomatidae. It could be occur in various forms that are medically known that would rather be muco-cutaneous or visceral leishmaniasis which appears to be most lethal or cutaneous ulcer lesions that is non-fatal and self-healing. The cases of leishmaniasis has significantly increased in last few years. Therefore leishmaniasis ranked in top six selected tropical diseases for research work by WHO [1]. Leishmania is a very mortal protozoan among the human protozoans after malaria in terms of infection [2]. It is a common disease in about 88 countries of South America, Europe, Asia and Africa continents [3].

Among these 88 countries there are 16 developed, 72 developing (including Pakistan, India and Iran) and 13 least developed countries [4]. More than 12 million cases has been reported by WHO in which 90% cases were found in Pakistan, Bangladesh, India, Afghanistan, Sudan, Algeria, Brazil and Nepal [1]. Among these cases VL became the cause of approximately 0.1 million deaths every year [5]. It has been estimated that 600,000 cases of visceral leishmaniasis and 1.5 million of cutaneous leishmaniasis are expected every year leaving behind almost 350 million people on threat WHO [3, 6].

GEOGRAPHICAL DISTRIBUTION OF *LEISHMANIA* SPECIES

Based on distribution in the gut of female sand fly, Leishmania can be divided into two subgenera. One is *Leishmania* (develops in midgut and foregut) and the second one is *Viannia* (develops in hindgut). The parasites of *Viannia* (subgenus of Leishmania) could only be find in new world where the species of Leishmania belongs to *L. mexicana complex (L. venezuelensis, L. amanuensis, L. mexicana), L. donovani complex (L. Archibald, L. infantum /chagasi, L. infantum, L. donovani)* and *L. tropica* complex (*L. major, L. aethiopica, L. tropica*) [7].

Table-1 represents the classification of Leishmania species along with its geographical distribution.

Table-1: Different Leishmania species and their Geographical distribution

Leishmania Complex	Specie	Disease	Geographical Distribution	Reference
L.Donovani	*L.Donovani*	Visceral Leishmaniasis (VL)	Sudan, East Africa and Asia	Bari *et al*., 2008
	L.infantum	Visceral Leishmaniasis (VL)	Mediterranean basin, India, China and Pakistan	Bari *et al*., 2008
	L.chagasi	Cutaneous Leishmaniasis (CL)	Brazil, Colombia, Central America	Bari *et al*., 2008
L.Tropica	*L.major*	Zoonotic Cutaneous (ZCL)	World wide	Khan *et al*., 2004
	L.Tropica	Anthroponotic Cutaneous(ACL)	World wide	Khan *et al*., 2004
	L.aethopica	Diffuse cutaneous (DCL)	East Africa and Yemen	Khan *et al*., 2004
L.Mexicana Complex	*L.amazonensis*	Cutaneous Leishmaniasis (CL)	Mexico, Guatemala, Honduras and Venezuela	Shaw *et al*., 1994
	L.pifanoi	Cutaneous Leishmaniasis (CL)	Mexico, Guatemala, Honduras and Venezuela	Shaw *et al*., 1994
	L.garnhami	Cutaneous Leishmaniasis (CL)	Mexico, Guatemala, Honduras and Venezuela	Shaw et al., 1994
	L.venzuelensis	Cutaneous Leishmaniasis (CL)	Mexico, Guatemala, Honduras and Venezuela	Shaw et al., 1994
L.Braziliensis	*L.guyanensis*	Cutaneous Leishmaniasis (CL)	Brazil, East Andes, Peru, Venezuela and Panama	Shaw et al., 1994
	L.braziliensis	Mucocutaneous Leishmaniasis (MCL)	Brazil, East Andes, Peru, Venezuela and Panama	Shaw et al., 1994
	L.peruvanis	Cutaneous Leishmaniasis (CL)	Brazil, East Andes, Peru, Venezuela and Panama	Shaw et al., 1994
	L.panamensis	Cutaneous Leishmaniasis (CL)	Brazil, East Andes, Peru, Venezuela and Panama	Shaw et al., 1994

LEISHMANIA GENOME

Most of *Leishmania* has diploid chromosome [8, 9]. About 22-33 numbers of chromosomes identified in the species of Leishmania which widely accepts the diploidy phenomenon and most of the chromosome having 20-25 pairs of chromosomal range could generally be find in old as well as new world species [10]. Though 36 numbers of chromosome are characterized in *L. infantum* and *L. donovani* species [11]. These chromosomes are linear having 200 to 4000 kb telomeres length with unidentified centromeres [12].

MORPHOLOGY OF LEISHMANIA

The intracellular Leishmania protozoan could morphologically be found in two major forms i.e. in Promastigotes or flagellar form in hindgut of sand fly and in protozoan culture while in non-flagellar form in monocytes of animal or human [2]. In macrophages of vertebrate hosts that are infected with Leishmania, there found Amastigote of about 2 to 4 µm having round to oval bodies. These are generally colorless and mainly surrounded by pellicle with a homogenous cytoplasm, central nucleus having small Kinetoplast anteriorly located near to flagella. This Kinetoplast is basically a section of mitochondria which contains mitochondrial DNA organized in fine fibrils [2]. Hematoxylin-eosin stain is used for the appearance of nucleus and Kinetoplast to be seen. Promastigotes form which has flagella could be seen in culture media and in sand fly's gut. This form is elongated (10-15 um length) and motile with anteriorly located flagellum. During initial phases of growth there observed clusters of Promastigotes which could also be known as rosette. In Amastigotes there found a layer of subpellicular fibrils sustained by double membrane. These fibrils express spiral movement from flagellar base to posterior apical end. These fibrils retains during transformation (Amastigotes to Promastigotes form) losing single membrane. In Amastigotes, there is a small out growth (9x2 fibril configuration) but no true flagellum near to kinetosome.

VECTOR SPECIE

The vector insect specie for Leishmania is sand fly having genus *Phlebotomus*, order Diptera, sub family *Phlebotominae* and family *Psychodidae*. It has a wide range of distribution around the world but generally found in dry and hot climatic zones of tropical regions. *Phlebotominae* (sub family of Leishmania) comprises 600 species with five genera. *Phlebotomus* is considered to be most pathogenic genera whereas species from the genera of *Lutzomyia*, *Phlebotomus* and *Sergentomyia* are mainly known for the transmission of Leishmaniasis. *Phlebotomus* in old world and

Lutzomyia in new world is responsible for the transmission of *Leishmania* parasite. Adult female sand fly is small insect with curved body, long hairy legs, upward erected wings, black and large eyes, grayish or yellowish in color with 2 to 5 mm length [13].

The habitat of sand flies is often warm and dry and they mostly interbreed in cracks in roofs and walls of houses, tree cracks, holes in river banks and streams, crevices and wild rodent holes in old world whereas Lutzomyia interbreed in forest litters [14]. Sand flies are nocturnal having weak flights but has a spanking characteristic of hopping to few meters from the ground avoiding rainy and windy seasons. Their eggs requires high humidity and are usually hatched in 5 to 20 days. Their larvae feeds on litters of domestic animals and rodents and also on organic matters for development. Under appropriate climatic conditions, sand flies complete their life cycle in 1 to 3 months. For the process of oviposition, female sand flies also need mammals' blood beyond the usual feed of plant nector. Because of this very reason only female sand fly is considerably responsible for the transmission of Leishmania parasite to the animal host. Based on the feeding pattern and nature of species, the old worlds' sand flies appears to be active during summer (June or July) and autumn (August or September).

CLINICAL FORMS OF LEISHMANIASIS

There are three main clinically known forms of leishmaniasis that are MCL (mucocutaneous leishmaniasis) caused by *L. donovani*, *L. infantum* and *L. major* in old world and by *L. braziliensis*, *L. guyanensis* and *L. panamensis* in new world, VL (visceral leishmaniasis) caused by *L. tropica and L. donovani* complex in old world and by *L. amazonensis* in new world and CL (cutaneous leishmaniasis) caused by *L. major*, *L. tropica*, *L. donovani* and *L. infantum* in Old World and by *L. mexicana* in New World. Beside these a distinct form of CL is considered the 4th form which is known as DCL (diffused cutaneous leishmaniasis) caused by *L. aethiopica* and *L. amazonensis* in old and new world respectively [15, 16]. The infection of CL start from small papule (erythematous) then develops into nodules and then into severe form of ulcerative lesions. Unusually sporotrichoid patterns is also observed clinically that subcutaneous nodules develops along with hyperkeratosis and lymphatics as well as lupoid leishmaniasis or leishmaniasis recidivans [17]. In Asian and Middle East countries the infection is almost impossible to be clinically differentiated that it is rather caused by *L. tropica* or *L. major* [18]. Kala-azar or VL (Visceral leishmaniasis) is mainly linked with progressive anemia, considerable loss of weight, hepatomegaly, splenomegaly and persistent fever. It appears to be mortal and much deadly because of secondary bacterial taints, if didn't treated on time [19]. PKDL (post Kala Azar dermal leishmaniasis) is a severe complication expresses after few years or months after the treatment of VL [5]. CL is also having another serious form known as MCL (Mucocutaneous leishmaniasis) which disfigures lesions of throat nose and face [4]. This appears commonly in nose and mouth and results in the destruction of cartilage and tissues [5]. When its lesion spread into deep mouth and larynx, it might affect the speech. Moreover some other signs like weight loss and can also be expressed. Besides these, secondary infections from bacteria in open sores are expected. DCL could result in chronic infection of skin and dispersed lesions having very much resemblance with lepromatous leprosy [17].

TREATMENT

CL lesions requires a spontaneous 8 to 12 months for healing. However, lesion on face (chin, lips, nose and cheeks) along with secondary fungal and bacterial infection create severe complications leaving no life for more than one year. Specific and timely treatment to such patients could be the only way for their healing [20]. For the treatment of CL, variety of therapeutic protocols are reviewed. Thermotherapy and cryotherapy are among the methods applied its treatment [21, 22]. The commonly practiced treatment all over the world for Leishmania is pentavalent antimonials injections in lesion for example sodium stibogluconate commercially known as Pentostam (Glaxowellcom) and meglumine antimonite with a commercial name of Glucantime (Aventis) [23]. Pentostan could be injected both intramuscularly (IM) or Interveinal (IV) and Glucantime could be injected IM or IL (intralesionally) depending upon the various stages of lesion. In case of IV treatment the patient is usually hospitalized and regular monitoring of liver enzymes is progressed. Various antifungal and antibacterial ointments could also be used. Paromomycin (aminindine) combined with that of methyl benzethonium chloride has profound result and appears more effective during L.major infection [18] from L. tropica. Very few cases are reported that took more than eight to twelve months of healing the lesions of lips and nose. The patients with new lesions (less than 3 to 4 weeks old) are usually advised to do not peruse treatment and wait for the correct timings of treatment to withstand an advanced immune system.

CONTROL

Various control measures for Leishmania are to destroy rodent holes and burrows, animal feed or to eliminate rodents and animal reservoirs as practiced prior in Tunisia and Jordan [18, 24]. It could easily be controlled by breaking the sequence of its life cycle in any stage. Various control methods might be adopted because one method may success in one environment but flops in another. It is more considerable in adopting any control method that it should be cost sufficient and it should be re applied or revised regularly after specific period of time. Another control measure for Leishmania is targeting the vector of sand fly. For the control of sand fly some measures like cracks covering in walls,

removal of litters and garbage near residential area and demolishing of breeding sites should be adopted. Insecticide should also be sprayed outside as well as inside of the houses especially in cracks and under windows. The risk of sand fly and Leishmania could also be reduced with the plantation an ornamental plant namely Bougainvillea glabra [25]. The use of insecticide like Deltamethrin and bed nets can reduce CL rate at a considerable proportion [26].

EPIDEMIOLOGY OF LEISHMANISIS

Global View of Leishmaniasis

It was estimated by WHO that leishmaniasis affected about 12 million individuals throughout the world. Out of these 1 to 2 million cases of CL and 450,000-650,000 cases of VL has been reported. Over 88 countries in the world are at risk of leishmaniasis leaving behind approximately 350 million folks on threat. The 90 % of VL cases reported from over 66 countries revealed that Sudan, Brazil, Bangladesh, Nepal and India are top five countries that are mostly affected. On the other hand report of the CL cases revealed that 90 % of CL cases were reported from seven countries that are Syria, Saudi Arabia, Iran, Peru, Brazil, Algeria, Afghanistan and Pakistan. It is summarized that Asian countries are the mostly targeted countries of leishmaniasis [27]. In addition 90 % of MCL cases are also reported from Brazil, Peru and Bolivia.

CL in neighboring countries of Pakistan

Based on the geographical territories of Pakistan all the three proposed forms of leishmaniasis are found in all the neighboring countries to which Pakistan shares its border in any respect i.e. China at the north east, Iran at south east, Afghanistan at north west and India at the east of Pakistan. Based on the prior reported cases from the neighboring countries of Pakistan it was revealed that VL is mostly endemic in India while CL is in Iran and Afghanistan.

Leishmaniasis in Afghanistan

Based on the persistent of CL in the neighboring countries of Pakistan, it was stated that CL is mostly reported from Iran and Afghanistan. Out of these the perseverance of CL most common in Afghanistan, therefore, Afghanistan is mainly besieged for CL form of leishmaniasis.

In Afghanistan the report from 10 selected villages (Herat) of eastern part, it was estimated that almost 20 % children has active lesions of CL mostly at Ghazni, Jalalabad and Kabul [28]. It was also delineated from school and house to house survey in Kabul, Afghanistan that total 875 individuals were having CL lesions. Out of these 667 were living in mountains base (mostly focused area of CL) while 135 in other places of the city [29]. The occurrence of CL was also studied by Nadim and Roastami [30] at the area of "Khair khana" near to Kabul city that was very much popular for CL outbreaks in 1972. Active lesions were 11.7 % and scares were 4.6 % in this study. It is revealed from a survey of various regions about the CL prevalence that there were 45.3 %, 26.4 % and 6.85 % scars and 2 %, 4.8 % and 3.1 % active lesions in Herat, Kandahar and Panjsher respectively [31]. According to Ashford [32] Visceral Leishmaniasis caused because of L. donovani was testified for the first time by Singh *et al*., [28] in Afghanistan. The transmission of ACL in Kabul was noticed to be occurred in homes according to Hewitt *et al*., [33]. The outbreaks of ZCL were confirmed by Faulde *et al*., [34, 35] for the first time in Mazar-e-Sharif province. They further extended their statement that Kabul is the most targeted city in regard of CL with an estimation of 67600 cases. In the year 2003 there were 16400 patients suffering from CL taking the treatment from six renowned hospitals of the city [22]. Over two millions of Afghan refugees are the possible carrier suspects currently live in Pakistan in regard of CL infection.

EPIDEMIOLOGY IN PAKISTAN

Visceral Leishmaniasis in Pakistan

Visceral Leishmaniasis (VL) is a periodic disease in Pakistan mostly at north east side especially in Gilgit Baltistan and AJK. In Pakistan VL is the most neglected disease in regard of research in subtropical and tropical regions. In these regions this was found most commonly in young children aging five to fifteen years and less commonly in adults. Conventional microscopic test or clinical diagnosis confirms that there are more cases in pervasive areas. But Pakistan has no primer medical facilitations for leishmaniasis. Many cases were diagnosed clinically and the medical community of Pakistan has published various clinical features not only at national but also at international level, yet there revealed no information about its vectors and reservoirs identity for both VL and CL. Leishmaniasis was very firstly reported in subcontinent of Indo-Pak before the creation of Pakistan in 1924 by Hance. After Hance some of the cases like spleen enlargement with fever along with positive aldehyde reaction in lab result were reported by Qutubuddin [36] at the civil hospital of DI Khan. In two cases Leishmania was observed there in punctures of spleen of the individuals actually hailing from the region near to Kohat having no travel history outside of the province. This was also furtherly confirmed by Nasir [37]. Similarly 35 VL cases were also reported by Ahmad *et al*., [38] from CMH (Combined Military Hospital) of Skardu and Northern area of "Baltistan". They explained that from 1957 to 1960, VL cases were observed in 25 children aging less than 16 years and 10 individuals aging 16-40. Most of such cases were from Kuru village, Shyok river and Indus region of north east Baltistan of "Northern areas" of Pakistan [39]. Burney *et al*., [40] stated 46 VL cases Yugo, Kunis, Khaplu, Thogu, Gwadi Keris, Kuru and Parkuta villages. It is proposed that VL has the existence at valleys of Shyok and river Indus since long ago. The old resident from

these areas gave the additional statement that this disease approached in waves appeared to be very deadly in children. VL has also the persistence in Chilas during eighth decade. However there were no active case reported from the proposed area in 1979. In the hospitals of Rawalpindi there were 14 VL cases of children hailing from KPK, AJK and Punjab during 1983-1985 [41]. The first VL case from Multan was reported by Noor *et al.*, [42]. At NIH (National Institute of Health), Islamabad, Rab *et al*., [43] reported 22 VL cases in which 4 were from Punjab and KPK, 15 from AJK and 3 from Gilgit having average age of 4.5 years. High level of antibodies were detected in all these cases in IFAT (Indirect immune fluorescent antibody technique). From the BM aspirates of all these patients the Leishmania Amastigotes isolated and the organism was termed as Leishmania infantum. Hassan *et al*., [44] reported 38 VL cases from Rawalpindi Medical college in which the majority were hailing from AJK (Muzaffarabad outskirts and Poonch), 4 cases came from Abbottabad, Rawalpindi and Murree and only two from Gilgit. In a review from Rab and Evans [45] it was revealed from the previous 10 years of record that total 239 VL cases was registered in the hospitals of Gilgit, Muzaffarabad, Rawalpindi and Islamabad. In these cases 86 % were in under 5 years age of children and 52 % were of 2 years of age. At the District Head Quarter Hospital, Timargara of district Dir Rahim *et al*., [46] reported 10 cases of VL in 2 to 10 years age of children. Likewise Nagi and Nasimullah [47] examined twenty patients of 1-9 years of ages that were admitted at Sandeman Provincial Hospital Quetta, Baluchistan (province) and were having the primer signs of VL. Glucantime (40 to 60 mg/kg/day) were injected to these patients up to four weeks on daily basis. In these patients only eight were being cured while the remaining three didn't sustained life. Twenty splenomegaly cases were also studied by Nawab *et al*., [48, 49] that were referred to the Laboratory of Dr. Ehsanullah at Karachi in which 4 were diagnosed clinically that they are having VL infection. However from central Punjab and Sindh there were no VL cases reported. Leishmania infantum has proved to be the major cause of VL in Himalayan area of Pakistan and is being isolated from 15 patients. In these one was isolated from spleen, three from skin and eleven from BM [43, 45].

Cutaneous Leishmaniasis in Pakistan

Khyber Pakhtunkhwa

The studies from KPK are case reports or prevalence studies from the medical community. Rowland *et al*., [50] ranked CL by Leishmania tropica as an emerging disease of KPK after studying the cases of ACL in a camp of Afghan refugees at the place of Timargara, Dir in KPK. At tribal zone of "Pak Afghan border", ACL is much endemic because it may transmit across the border from Afghanistan (Mostly endemic country of ACL). Hamid and Ali [51] observed 57 CL cases at Waziristan agency with a ratio of 3:1 (male to female) by investigating 1370 folk. Various CL cases from Dir district were reported by Rahim *et al*., [52] and in that year (2003) he also reported 58 patients of CL including Army personals along with civilians at Kohat. The average duration for lesion was 5 to 7 months and were having the diameter of 1 to 3 cm. Brooker *et al*., [53] and Kolaczinski *et al*., [54] inspected ACL Epidemiology at border areas of Afghanistan and Pakistan Including Tribal areas and exposed that there were 2.4 to 2.7 % ACL scars and lesions in the folks. Similarly in 2004, a study at the camps of Afghan refugee and the local Pakistani community near to these camps, ACL prevalence was notified as 1.7 % in the local community near to these camps. It was also observed that the risk of ACL is mostly related with age and have no association with gender. During 2002 (January to May) the data taken from the hospitals in Peshawar revealed that there were 16 CL cases confirmed in laboratory from 167 males and 6 CL cases from 139 females.

Baluchistan

CL is mostly found in every province of Pakistan including Baluchistan. Initially a survey was conducted by Khan and Rafique [55] for CL. This survey was actually conducted in October 1979 and they reported that CL is a very rare type disease at the capital city (Quetta) of Baluchistan. Only 4.9 % of prevalence was recorded in district hospital of Sibi, Baluchistan. Mewand, Gumbz, Sangsela, Kohlu, Dera Bugti and Lehri was the most endemic areas of Baluchistan for CL. Total 100 of CL patients were reported by Jan, 1984 in which 8 were from Lehri, 15 from Duki, 12 from Kohlu, 20 from Lasbella and 45 were Afghan refugees. According to this report females were less affected than males and 75 % children under 15 were mainly affected. Rab *et al.*, [56] studied 418 children of schools aging from 5 to 15 years in Uthal and Lasbella districts. In these cases, 05 patients were having active lesion while 112 were having scars of CL. Ahmad [57] reported various cases of CL from the southern part of Baluchistan. A survey conducted in 1995-96 by combined efforts of DSTO (Defense Science and Technology Organization) and AMC (Army Medical College) of Baluchistan revealed that there were 50 cases of CL in Army soldiers [58]. Kakarsulemankhel [59] stated that Baluchistan is having two kinds of CL i.e. ZCL and ACL. A survey conducted in 1996 to 2001 revealed that there were 8 and 31 CL cases in old and new foci respectively in Baluchistan Kakarsulemankhel [60]. It was furtherly explained that 45.6 % of CL prevalence was noted in young children under the age of 10. Imran *et al.*, [61] also studied CL incidence among the families of armed forces living in Sibi. Total 293 case were studied in which 96.6 % were males and 3.4 % were females.

Punjab

Various cases of CL were also reported from Punjab but there is very less published literature

available for this province. Malik *et al*., [62] reported 2500 CL cases from Nashtar Hospital, Multan. Mujtaba and Khalid [63] also reported nature of 305 suspects from the same hospital surveyed in 1995-97 and it was observed all these suspects were having dry lesions. Other CL cases were also reported by Ayub *et al.,* [64] in Multan. Department of dermatology of "Nashtar Medical College" confirmed 173 CL cases between December 1999 and March 2000 [65]. All the patients were hailing from old city of Multan. In the investigating groups from 6 to 35 years of age's individuals 86 % patients belongs to the group of children from 11 to 12 years of ages. Females were having less lesions than males (77 %).

Sindh

From Sindh province a lot of research work has been done on prevalence and molecular studies as compared to other provinces. Nawab *et al.,* [66] reported 90 out of 120 confirmed cases of suspected patients referred to Dr. Ehsanullah's Laboratory Karachi for lab diagnosis. The first reported cases of CL from a village Sono Khan Chandio of mountainous belt of Larkana district, Sindh province was from Pathan and Soomro [67]. 115 out of 130 patients were confirmed for having CL by microscopy. The cases of CL were reported from many districts of Sindh province such as Larkana, Jacobabad, Qambar Ali Khan, Shahdad Kot, Dadu Miro Khan, and Warah. Bhutto *et al.,* [68] Soomro *et al.,* [67] described case records of 478 suspected CL patients reporting to Chandka Medical College Hospital, Larkana during 2001 and the disease was confirmed in 68 percent of children as compared to adults. About 77 percent of the lesions are open infected ulcers followed by other types of clinical presentations like nodular plaques and papules. In another study conducted in 2003 by Bhutto *et al*., [69], who detected new endemic foci of CL in Sindh province. Soomro *et al.,* [70] reported an outbreak of 200 cases of CL at a small village Ghaibi Dero of Larkana district, Sindh. According to findings the outbreak was proposed to be the immigration of people to this village from endemic areas of Baluchistan and also to the adjoining parts of upper Sindh province [69]. Kolachi *et al.,* [71] studied 236 cases in Taluka Juhi, district Dadu and was concluded that the sudden upsurge in number of CL cases was of the fact that disease was brought to Juhi from Baluchistan Province and Afghanistan as this district share borders with Talaku where large number of people are either Afghan refugees or migrants from Baluchistan. Bhutto *et al.*,[72] studied clinical presentation of 1640 CL suspected patients referred to Chandka Medical College, the lesions were of different nature like dry ulcerative, wet ulcerative, and crusted lesions. The prevalence of CL in Pakistan is usually underestimated mainly because of lack of case reporting system and misdiagnosis. The cases occurred sporadically throughout the year but form the last few years the geographical boundaries of disease have extended. The disease that was thought to be only endemic in Baluchistan has become considerably prevalent in other provinces of Pakistan like Sindh and Khyber Pukhtankhwa and some parts of Punjab.

LEISHMANIA SPECIES RESPONSIBLE FOR CL IN PAKISTAN

For the very first time in "Sono Khan", Sindh, Pakistan it was reported that the infection comes from *Trypanosoma* species [73]. Pakistan have no confirmed vector for CL but based on the fauna of sand fly in Afghanistan (neighboring country) it could be presumed that *P. sergenti* is much possible vector for CL and zoonotic CL could come from *P. salehi* or *P. papatasi* in KPK [74]. A research work on the sand flies in various villages of district Dir of KPK by Rowland *et al.,* [50], the proposed vector for CL was reported to be *P. sergenti*. Rowland *et al.,* [50] and Killick- Kendrick *et al.,* [74] confirmed that the vector for *L. tropica* in Afghanistan is *P. sergenti*, so it could be in Pakistan also especially in KPK. The vector specie for *L. major* is confirmed to be *P. papatasi* in Iran [75, 76] and this is also having the probability in Pakistan. *P. alexandri* which is reported in rural Iran [77] is also confirmed in Pakistan. Recently collected endemic foci for CL in DG Khan Rowland *et al.,* [50] and Punjab [78] strongly confirmed that the above stated species are the primer possible vectors for Leishmaniasis in Pakistan.

PROVED LEISHMANIA SPECIES IN PAKISTAN

Rab *et al*., [45] concluded that in Pakistan, the ACL is mainly caused by *L. tropica*, by isolating it from cutaneous lesions of 13 selected patients. Rowland et al. confirmed this by culturing *L. tropica* on molecular basis from the camp of afghan refugees at Dir (KPK). Marco *et al*., [79] typed two species of Leishmania that are *L. major and L. tropica* from various altitudes of Baluchistan (Quetta and Sibi) province of Pakistan. Rab *et al*., [45] furthermore typed L. infantum from patients of VL hailing from Northern areas of the Pakistan, and unluckily there is research work reported on Leshmenia genotyping in KPK and most importantly at its southern region.

CONCLUSION

This review concludes that Cutaneous Leishmaniasis is much prevalent in Pakistan especially in Khyber Pakhtunkhwa and Fata and the main source of its prevalence are domestic animals, migrations, refugee camps, non-availability of the treatment/ medicines and clinics, awareness campaigns and the poor economy level of the targeted areas. The adoption of precautionary measures for the disease should be proper wearing clothes covering full body parts, use of mosquito repellents and mosquito nets. More provision of the safety should be adopted by males and children under fifteen as it is more prevalent in males than females and in children under the age of fifteen than adults. The availability of Glucantime at government hospitals for rural areas could be a great investment of

the government for this disease as this is the most reliable but expensive treatment of the proposed disease.

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REFERENCES

1. World Health Organization (WHO). (2001). Communicable disease profile: Afghanistan and neighboring countries. Geneva: WHO.
2. Chang, K. P., Fong, D., & Bray, R. S. (1985). Biology of Leishmania and leishmaniasis. In: Chang K.P., R.S. Bray, eds. Leishmaniasis: Human Parasitic Diseases, Vol. 1. Philadelphia: Elsevier.1-30.
3. World Health Organization (WHO). (1998). Life in the twenty century: A vision for all. World Health Organization (WHO). (2001). Afghanistan crisis special report, Leishmaniasis in Pakistan .World Health Organization Geneva, Switzerland.
4. Desjeux, P. (1996). Leishmaniasis Public health aspects and control. Clin. Dermatol. 14: 417-23.
5. Ashford, R. W. (2000). The leishmaniasis as emerging and reemerging zoonosis. Int. J. Parasitol. 30: 1269-128.
6. World Health Organization (WHO). (2005). PCR based diagnosis of cutaneous Leishmaniasis.
7. Shaw, J. J. (1994). Taxonomy of the genus Leishmania: present and future trends And their implications. Mem. Ins. Oswaldo. Cruz. Rio de Janeiro. 89(3): 471-478.
8. Beverly, S. M., Ismach, R. B., & McMahon-Pratt, D. (1987). Evaluation of the Genus Biochem. Cell Biol. 73: 235-240.
9. Wong, A. K. C. (1995). Molecular genetics of the parasitic protozoans Leishmania. Parasitol. 30: 1269-128.
10. Mendoza-León, A., Shaw, J. J., & Tapia, F. J. (1996). A guide for the cutaneous leishmaniasis connoisseur. In *Molecular and Immune Mechanisms in the Pathogenesis of Cutaneous leishmaniasis* (pp. 1-23). RG Landes Bioscience Publishers, Austin, Texas.
11. Webb, J. R., Button, L. L., & McMaster, W. R. (1991). Heterogeneity of the genes encoding the major surface glycoprotein of Leishmania donovani. *Molecular and biochemical parasitology*, *48*(2), 173-184.
12. Lighthall, G. K., & Giannini, S. H. (1992). The chromosomes of Leishmania. *Parasitology Today*, *8*(6), 192-199.
13. Kakarsulemankhel, J. K. (2004). Present situation of cutaneous leishmaniasis in Balochistan, Pakistan. *Pak J Biol Sci*, *7*(5), 698-702.
14. Pandey, K., Pant, S., Kanbara, H., Shuaibu, M. N., Mallik, A. K., Pandey, B. D., ... & Yanagi, T. (2008). Molecular detection of Leishmania parasites from whole bodies of sandflies collected in Nepal. *Parasitology research*, *103*(2), 293.
15. Ben-Ami, R., Schnur, L. F., Golan, Y., Jaffe, C. L., Mardi, T., & Zeltser, D. (2002). Cutaneous involvement in a rare case of adult visceral leishmaniasis acquired in Israel. *Journal of Infection*, *44*(3), 181-184.
16. Bulle, B., Millon, L., Bart, J. M., Gállego, M., Gambarelli, F., Portús, M., ... & Piarroux, R. (2002). Practical approach for typing strains of Leishmania infantum by microsatellite analysis. *Journal of Clinical Microbiology*, *40*(9), 3391-3397.
17. ul Bari, A., Hasshim, R., Mahmood, K., Muhammad, I., Shahbaz, N., & Tariq, K. M. (2016). Clinico-epidemiological pattern of cutaneous leishmaniasis in armed forces personnel fighting war against terrorism in Khyber Pakhtunkhwa Province and Fata regions. *Journal of Pakistan Association of Dermatology*, *21*(1), 10-15.
18. Klaus, S., & Frankenburg, S. (1999). Cutaneous leishmaniasis in the Middle East. *Clinics in dermatology*, *17*(2), 137-141.
19. Sundar, S., & Rai, M. (2002). Laboratory diagnosis of visceral leishmaniasis. *Clinical and diagnostic laboratory immunology*, *9*(5), 951-958.
20. Dowlati, Y. (1996). Cutaneous Leishmaniasis: Clinical Aspect. Clin. Dermatol. 14: 425- 431.
21. Al-Majali, O., Routh, H. B., Abuloham, O., Bhowmik, K. R., Muhsen, M., & Hebeheba, H. (1997). A 2-year study of liquid nitrogen therapy in cutaneous leishmaniasis. *International journal of dermatology*, *36*(6), 460-462.
22. Reithinger, R., & Coleman, P. G. (2007). Treating cutaneous leishmaniasis patients in Kabul, Afghanistan: cost-effectiveness of an operational program in a complex emergency setting. *BMC infectious diseases*, *7*(1), 3.
23. World Health Organization (WHO). 1990. Control of the Leishmaniasis. Technical Report series 793. Geneva: WHO.
24. Ashford, S. J., & Black, J. S. (1996). Proactivity during organizational entry: The role of desire for control. *Journal of Applied psychology*, *81*(2), 199.
25. Schlein, Y., Jacobson, R. L., & Müller, G. C. (2001). Sand fly feeding on noxious plants: a potential method for the control of leishmaniasis. *The American journal of tropical medicine and hygiene*, *65*(4), 300-303.
26. Alten, B., Caglar, S. S., Kaynas, S., & Simsek, F. M. (2003). Evaluation of protective efficacy of K-

OTAB impregnated bednets for cutaneous leishmaniasis control in Southeast Anatolia-Turkey. *Journal of vector ecology: journal of the Society for Vector Ecology*, *28*(1), 53-64.

27. Kumar, R., Bumb, R. A., Ansari, N. A., Mehta, R. D., & Salotra, P. (2007). Cutaneous leishmaniasis caused by Leishmania tropica in Bikaner, India: parasite identification and characterization using molecular and immunologic tools. *The American journal of tropical medicine and hygiene*, *76*(5), 896-901.
28. Singh, M., Arya, L. S., Aram, G. N., Fazal, M. I., Qureshi, M. A., & Goel, R. G. (1982). Kala-azar in Afghanistan. *The Journal of tropical medicine and hygiene*, *85*(5), 201-204.
29. Omar, A., Saboor, A., Amin, F. M., & Sery, V. (1969). Preliminary study on the foci of cutaneous leishmaniasis in Kabul City. *Zeitschrift fur Tropenmedizin und Parasitologie*, *20*(pt. 3).
30. Nadim, A., & Rostami, G. S. (1974). Epidemiology of cutaneous leishmaniasis in Kabul, Afghanistan. *Bulletin of the World Health Organization*, *51*(1), 45.
31. Nadim, A., Javadian, E., Noushin, M. K., & Nayil, A. K. (1979). Epidemiology of cutaneous leishmaniasis in Afghanistan. Part 2. Anthro-ponotic cutaneous leishmaniasis. *Bulletin de la Société de Pathologie Exotique*, *72*(5/6), 461-466.
32. Ashford, A. J., & Pain, V. M. (1986). Effect of diabetes on the rates of synthesis and degradation of ribosomes in rat muscle and liver in vivo. *Journal of Biological Chemistry*, *261*(9), 4059-4065.
33. Hewitt, S., Reyburn, H., Ashford, R., & Rowland, M. (1998). Anthroponotic cutaneous leishmaniasis in Kabul, Afghanistan: vertical distribution of cases in apartment blocks. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *92*(3), 273-274.
34. Faulde, M., Schrader, J., Heyl, G., Amirih, M., & Hoerauf, A. (2008). Zoonotic cutaneous leishmaniasis outbreak in Mazar-e Sharif, northern Afghanistan: an epidemiological evaluation. *International Journal of Medical Microbiology*, *298*(5-6), 543-550.
35. Faulde, M., Schrader, J., Heyl, G., Amirih, M., & Hoerauf, A. (2008). Zoonotic cutaneous leishmaniasis outbreak in Mazar-e Sharif, northern Afghanistan: an epidemiological evaluation. *International Journal of Medical Microbiology*, *298*(5-6), 543-550.
36. Qutubuddin, M. (1951). Uranotaenia mattinglyi sp. N., a new species of mosquito (diptera, culicidae) from hyderabad (deccan), india. *Systematic Entomology*, *20*(9-10), 107-109.
37. Nasir, A. (1958). Sand flies of West Pakistan. Pakistan J. Heal. 21: 35-39.
38. Ahmed, N., Burney, M. I., & Wazir, Y. (1960). A preliminary report on the study of kala-azar in Baltistan (West Pakistan). *Pakistan Armed Forces Medical Journal*, *10*, 1-10.
39. Ahmad, N., & Burney, M. I. (1962). Leishmaniasis in northern areas of Pakistan. Pak. Arm. Force Med. J. 12: 1-11.
40. Burney, M. I., Wazir, Y., & Lari, F. A. (1979). A longitudinal study of visceral leishmaniasis in northern areas of Pakistan. *Tropical Doctor*, *9*(3), 110-116.
41. Saleem, M., Anwar, C. M., & Malik, I. A. (1986). Visceral leishmaniasis in children: a new focus in Azad Kashmir. *Journal of the Pakistan Medical Association*, *36*, 230-233.
42. Noor, N. A., Qazi, A. W., Saleem, M., Masood, M., & Ahmad, Z. (1986). Kala-azar in Multan (a case report). *JPMA. The Journal of the Pakistan Medical Association*, *36*(8), 212-213.
43. Rab, M. A., Iqbal, J. A. M. S. H. A. I. D., Azmi, F. H., Munir, M. A., & Saleem, M. O. H. A. M. M. A. D. (1989). Visceral leishmaniasis: a seroepidemiological study of 289 children from endemic foci in Azad Jammu and Kashmir by indirect fluorescent antibody technique. *JPMA. The Journal of the Pakistan Medical Association*, *39*(9), 225-228.
44. Shah, S. H., & Hassan, M. (1995). Visceral leishmaniasis-a study of 38 cases on the basis of geographical distribution.
45. Rab, M. A., Frame, I. A., & Evans, D. A. (1995). The role of dogs in the epidemiology of human visceral leishmaniasis in northern Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *89*(6), 612-615.
46. Rahim, F., Jamal, S., Raziq, F., Uzair, M., Sarwar, B., Ali, H., & Sherin, M. (2011). An outbreak of Cutaneous Leishmaniasis in a village of district Dir, NWFP. *Journal of Postgraduate Medical Institute (Peshawar-Pakistan)*, *17*(1).
47. Nagi, A. G., & Nasimullah, M. (1993). Visceral leishmaniasis in Balochistan. *Pakistan pediatric journal*, *17*(1), 7.
48. Nawab, H., Ehsanullah, S., Haider, W., & Khanani, R. (1996). Visceral leishmaniasis in Karachi. Pakistan J. Med. Sci. 12: 217-220.
49. Nawab, H., Ehsanullah, S., Haider, W., & Khanani, R. (1997). Visceral Leishmaniasis in Karachi. Pakistan J. Med. Sci. 13: 383-388.
50. Rowland, M., Munir, A., Durrani, N., Noyes, H., & Reyburn, H. (1999). An outbreak of cutaneous leishmaniasis in an Afghan refugee settlement in north-west Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *93*(2), 133-136.
51. Hamid, A., & ALI, J. (2002). Leishmaniasis in North Waziristan Agency NWFP, Pakistan. *Pakistan journal of zoology*, *34*(2), 173-174.
52. Rahim, F., Jamal, S., Raziq, F., Uzair, M., Sarwar, B., Ali, H., & Sherin, M. (2011). An outbreak of Cutaneous Leishmaniasis in a village of district

Dir, NWFP. *Journal of Postgraduate Medical Institute (Peshawar-Pakistan)*, *17*(1).

53. Brooker, S., Mohammed, N., Adil, K., Agha, S., Reithinger, R., Rowland, M., ... & Kolaczinski, J. (2004). Leishmaniasis in refugee and local Pakistani populations. *Emerging infectious diseases*, *10*(9), 1681.
54. Kolaczinski, J., Brooker, S., Reyburn, H., & Rowland, M. (2004). Epidemiology of anthroponotic cutaneous leishmaniasis in Afghan refugee camps in northwest Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *98*(6), 373-378.
55. Khan, G. S., & Rafique, M. (1980). Technical guide for chemical analysis of soil and water. *Soils bulletin*, (14), 54-55.
56. Fiori, C., & Devine, R. A. B. (1986). Evidence for a wide continuum of polymorphs in a-SiO 2. *Physical Review B*, *33*(4), 2972.
57. Ahmad, N., & Venkatesan, S. (1988). Nef protein of HIV-1 is a transcriptional repressor of HIV-1 LTR. *Science*, *241*(4872), 1481-1485.
58. Iqbal, M. Z. (1998). A study of cutaneous leishmaniasis in Baluchistan, Pakistan: a forgotten Diseases of the tropics. Punjab University J. Zool. 13: 115-121.
59. Kakarsulemankhel, J. K. (2002). The Fauna of the Phlebotomine Sand flies (Diptera: Psychodidae, Phlebotominae) of Baluchistan, Pakistan and the Disease Cutaneous Leishmaniasis. Ph.D. Thesis. 1-389. Department of Zoology, University of Baluchistan, Quetta, Pakistan.
60. Kakarsulemankhel, J. K. (2004). Re-description of species of Sand flies of the sub Genus Phlebotomus (Diptera: Psychodidae) of Baluchistan, Pakistan. Pakistan J. Zool. 36: 143-164.
61. Ahmad, I., Humayun, Z., & Ahmad, M. (2008). Pattern of cutaneous leishmaniasis cases among troops and their families in Sibi. *Pak Armed Forces Med J*, *59*, 209-12.
62. Malik, G. Q., Khatoon, N., & Khan, M. A. (1973). Dermal leishmaniasis in Multan. Rawal. Med. J. 5: 134-139.
63. Mujtaba, G., & Khalid, M. (1998). Cutaneous Leishmaniasis in Multan, Pakistan. Int. J. Dermatol. 37(11): 843-845.
64. Ayub, S., Khalid, M., Mujtaba, G., & Bhutta, R. A. (2001). Profile of patients of cutaneous leishmaniasis from Multan. *Journal-Pakistan Medical Association*, *51*(8), 279-281.
65. Ayub, S., Gramiccia, M., Khalid, M., Mujtaba, G., & Bhutta, R. A. (2003). Cutaneous leishmaniasis in Multan: species identification. *JPMA. The Journal of the Pakistan Medical Association*, *53*(10), 445-447.
66. Nawab, H., Hafiz, A. Ehsanullah, S., Haider, W., & Khanani, R. (1997). Visceral Leishmaniasis in Karachi. Pakistan J. Med. Sci. 13: 383-388.
67. Soomro, F. R., Pathan, G. M., & Soomro, R. A. (2002). The patterns of cutaneous leishmaniasis and Differential diagnosis of misdiagnosed cases in Larkana region. J. Pakistan Assoc. Dermatol. 12: 77-82.
68. Bhutto, A. M., Soomro, F. R., Nonaka, S., & Hashiguchi, Y. (2001). Detection of new endemic areas Cutaneous leishmaniasis in Pakistan. In: Hashiguchi, Y. (ed.), Studies of the New Leishmaniasis and its Transmission with Particular Reference to Ecuador, pp: 146-153. Res. Rept. Ser. No. 6. Kyowa Printing and Co. Ltd, Kochi, Japan.
69. Bhutto, A. M., Soomro, F. R., Nonaka, S., & Hashiguchi, Y. (2003). Detection of new endemic areas of cutaneous leishmaniasis in Pakistan: a six year study. Int. J. Dermatol. 42: 543-548.
70. Soomro, F. R., Pathan, G. M., Bhutto, A. M., Bhatti, N. S., Abbasi, P., Kumari, M., Sheikh, S., Baloch, J. H., Katakura, K., Nonaka S., & Hashiguchi, Y. (2004). A preliminary survey of Cutaneous leishmaniasis at village Gaibi Dero in Larkana district, Sindh, Pakistan.
71. Kolachi, N. F., Kazi, T. G., Wadhwa, S. K., Afridi, H. I., Baig, J. A., Khan, S., & Shah, F. (2011). Evaluation of selenium in biological sample of arsenic exposed female skin lesions and skin cancer patients with related to non-exposed skin cancer patients. *Science of the Total Environment*, *409*(17), 3092-3097.
72. Bhutto, A., & Morley, J. E. (2008). The clinical significance of gastrointestinal changes with aging. *Current Opinion in Clinical Nutrition & Metabolic Care*, *11*(5), 651-660.
73. Kato, Y., Okami, M., Tajima, R., Fujita, D., & Kobayashi, N. (2010). Root response to aerobic conditions in rice, estimated by Comair root length scanner and scanner-based image analysis. *Field crops research*, *118*(2), 194-198.
74. Killick-Kendrick, R., Killick-Kendrick, M., & Tang, Y. (1995). Anthroponotic cutaneous leishmaniasis in Kabul, Afghanistan: the high susceptibility of Phlebotomus sergenti to Leishmania tropica. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *89*(5), 477.
75. Parvizi, J., Rapuri, V. R., Saleh, K. J., Kuskowski, M. A., Sharkey, P. F., & Mont, M. A. (2005). Failure to resurface the patella during total knee arthroplasty may result in more knee pain and secondary surgery. *Clinical Orthopaedics and Related Research®*, *438*, 191-196.
76. Parvizi, J., Ghanem, E., Menashe, S., Barrack, R. L., & Bauer, T. W. (2006). Periprosthetic infection: what are the diagnostic challenges?. *JBJS*, *88*(suppl_4), 138-147.
77. Yaghoobi-Ershadi, M. R., Javadian, E., & Tahvildare-Bidruni, G. H. (1995). Leishmania major MON-26 isolated from naturally infected Phlebotomus papatasi (Diptera: Psychodidae) in Isfahan Province, Iran. *Acta tropica*, *59*(4), 279-282.

78. Kakar, M. N., & Kakarsulemankhel, J. K. (2008). Prevalence of endo (trematodes) and ecto-parasites in cows and buffaloes of Quetta, Pakistan. *Pakistan Veterinary Journal*, *28*(1), 34.
79. Marco, J. D., Bhutto, A. M., Soomro, F. R., Baloch, J. H., Barroso, P. A., Kato, H., ... & Hashiguchi, Y. (2006). Multilocus enzyme electrophoresis and Cytochrome b gene sequencing–based identification of Leishmania isolates from different Foci of Cutaneous Leishmaniasis in Pakistan. *The American journal of tropical medicine and hygiene*, *75*(2), 261-266.