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REVIEW ARTICLE

Clinical Burden of Kala-azar in Bangladesh: A Review Update

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Abstract

Kala-azar is a tropical disease. There are an estimated 500,000 new cases of VL and more than 50,000 deaths from the diseases each year. The majority (>90%) of cases occur in just six countries like Bangladesh, India, Nepal, Sudan, Ethiopia and Brazil. Severe VL epidemics have been reported in the past. Since 1990, South Asia has experienced a resurgence of the lethal parasitic disease visceral leishmaniasis (VL). The disease has been reported from 109 districts of three countries. An estimated 190 million people are at risk of infection. The actual incidence rate of the disease is estimated to be about 8-10 times higher than the reported one in all three countries. There is an increasing trend of VL cases in India and fluctuating trends were found in Nepal and Bangladesh. Multi centric studies were conducted in Bangladesh, India and Nepal and major findings were that the current burden of disease is 20 times higher than the elimination target in 2010/2015. Kala-azar has appeared to have spread along the courses of the Ganges and Brahmaputra rivers. In these early outbreaks, the case-fatality rate was reported to be >95 percent, with community-wide mortality rates of >25 percent. This review has focused on the clinical burden of kala-azar in Bangladesh. [J Sci Found, 2012;10(2):70-79]

Keywords: kala-azar, leishmaniasis, clinical burden, review

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Introduction

Leishmaniasis is a chronic inflammatory disease of the skin, mucous membrane, or viscera caused by obligate intracellular, kinetoplastoid protozoan parasites transmitted through the bite of infected sandfly (Kumar et al., 2004).It is characterized by diversity and complexity (Desjeux, 2001). The disease is caused by the protozoa Leishmania that are transmitted by sand flies of the genera Phlebotomus (Old World Leishmaniasis) and Lutzomyia (New World Leishmaniasis). The clinical presentation ranges from simple cutaneous lesions to life threatening visceral forms. Visceral leishmaniasis - also known as kala azar - is characterized

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by irregular bouts of fever, substantial weight loss, swelling of the spleen and liver, and anaemia (occasionally serious). If left untreated, the fatality rate in developing countries can be as high as 100% within 2 years. (WHO, 2009).Kala-azar is also known as black sickness or fever, sarkari disease, Burdwan fever, Dum Dum fever after the district in Kolkata, where *L. donovani* was first found in an autopsy (Bahr and Bell, 1987).

History of Kala-azar in Bangladesh

Representations of skin lesions and facial deformities have been found on pre-Inca potteries from Ecuador and Peru dating back to the first century AD. There is evidence that cutaneous and mucocutaneous forms of leishmaniasis prevailed in the New World as early as this period. (WHO 2009). On the other hand kala-azar was first recognized as a specific disease in India. The term kala-azar was derived from Indian words Kala and Azar, meaning, "black sickness"; an illness in which the colour of the skin turns black. The word Kala also means "deadly"; thereby –signifying fatal illness (Chatterjee, 1980). The organism of VL or kala-azar was first described by Sir William Leishman. In 1901, Leishman identified certain organisms in smears taken from the spleen of a patient who had died from "dum-dum fever". At the time "Dum-dum", a town not far from Calcutta, was considered to be particularly unhealthy. The disease was characterized by general debility, irregular and repetitive bouts of fever, severe anaemia, muscular atrophy and excessive swelling of the spleen. Initially, these organisms were considered to be trypanosomes, but in 1903 Captain Donovan described them as being new. The link between these organisms and kala-azar was eventually discovered by Major Ross, who named them Leishmania donovani (WHO 2009). Leonard Rogers was first successful in culturing the parasite and showed that the flagellated form developed in culture. White Patton (1907) proved that amastigote stage could be found in wondering histiocytes of the peripheral blood and promastigote form occurred in the intestine of insect fed upon kala-azar patients. A similar parasite were observed in a disease of children in the Mediterranean countries by Nicole in 1908, proposed the name of infantile kala-azar for this disease and designated the parasite as *L. infantum* (Chatterjee, 1980).Further investigation revealed that it was a strain of *L. donovani*. The parasite of South American VL originally named as *L. chagasi* in 1937, was also found to be identical to L. donovani. In 1940, it was demonstrated that the Phlebotomus argentipes was the vector of India kala-azar (Birley, 1993).

Epidemiology

Leishmaniasis has been considered a tropical affliction that constitutes one of the six entities on the World Health Organization tropical disease research (WHO, TDR) list of most important diseases (Desjeux 2001). It occurs in 88 countries in tropical and temperate regions, 72 of them developing or least developed. An estimated 350 millions population is at risk and 10 million people are affected from this disease worldwide (Desjeux 1992). Two million cases occur annually, however, there is a gross under reporting of the cases from endemic regions, and there has been a progressive increase in the case of leishmaniasis being reported from the newer areas (Bora 1999). There are an estimated 500,000 new cases of VL and more than 50,000 deaths from the diseases each year (Desjeux 2004) a death toll that is surpassed among the parasitic diseases only by malaria (WHO, 2002). The majority (>90%) of cases occur in just six countries: Bangladesh, India, Nepal, Sudan, Ethiopia and Brazil. Migration, lack of control measures and HIV-VL co-infection are the three main factors driving the increased incidence of VL (Boelaert et al., 2000; Desjeux 2001). Severe VL epidemics have been reported in the past: in Southern Sudan, in a context of civil war and famine. VL killed an estimated 100000 people out of a population of 280,000 between 1984

and 1994 (Seaman et al., 1996). VL has developed epidemic cycles taking place almost regularly every 15-20 years (Alvar, 2006). Since 1990, South Asia has experienced a resurgence of the lethal parasitic disease visceral leishmaniasis (VL). India, Bangladesh, and Nepal account for an estimated 300,000 cases annually and 60% of the global burden of the disease. The disease has been reported from 109 districts (45 in Bangladesh, 52 in India and 12 in Nepal) of three countries. An estimated 190 million people are at risk of infection (Sundar et al., 2008). The actual incidence rate of the disease is estimated to be about 8-10 times higher than the reported one in all three countries (Singh et al., 2006). There is an increasing trend of VL cases in India and fluctuating trends were found in Nepal and Bangladesh. Multi centric studies were conducted in Bangladesh, India and Nepal and major findings were that the current burden of disease (21cases/10,000 population) is 20 times higher than the elimination target in 2010/2015 (Joshi et al.,2008). The parasitic disease kala-azar was first described in 1824, in Jessore district, Bengal in what is now Bangladesh (Sengupta 1947; Sanyal 1985). Historical records describe the classical picture of kala-azar-prolonged irregular fever, progressive emaciation, and enlargement of the liver and spleen (Sengupta 1947). Kala-azar appeared to have spread along the courses of the Ganges and Brahmaputra rivers (Sanyal 1985). In these early outbreaks, the case-fatality rate was reported to be >95 percent, with community-wide mortality rates of >25 percent. The epidemic that occurred in Jessore from 1824 to 1827 reportedly killed 75,000 people. Kala-azar epidemic peaks were recorded in Bengal in the 1820s, 1860s, 1920s, and 1940s (Birley 1993). In the 1920s, the All-Bengal Kala-azar Conference listed the districts most affected by kala-azar based on dispensary records as Tangail (in 1919), Rajshahi, Jessore, Mymensingh, and Noakhali (Birley, 1993). An intensive control programme aimed at the eradication of malaria was mounted in the 1950s and 1960s throughout the South Asian subcontinent.

Table 1: District and Year wise Kala-azar Report of Bangladesh

No	Name of districts	2001	2002	2003	2004	2005	2006	2007
1	Panchagar	94	16	23	15	0	10	20
2	Thakurgaon	29	25	11	14	8	9	13
3	Dinajpur	40	23	37	20	22	17	11
4	Rangpur	0	0	0	0	7	10	0
5	Gaibandha	8	11	17	20	14	15	6
6	Bogra	1	0	20	6	9	10	16
7	Joypurhat	10	15	9	7	7	7	16
8	Sirajganj	151	215	167	225	217	149	141
9	Pabna	733	658	503	431	434	375	279
10	Natore	170	525	195	209	139	83	169
11	Naogaon	115	883	175	123	107	129	157
12	Nawabganj	68	92	187	18	59	71	53
13	Rajshahi	70	69	59	117	74	37	129
14	Kustia	0	1	0	3	1	2	0
15	Jhenaidah	22	33	25	40	35	21	37
16	Jessore	1	0	0	0	0	0	0
17	Magura	0	63	1	0	0	0	0
18	Patuakhali	47	25	19	15	23	24	25

Table 1: District and Year wise Kala-azar Report of Bangladesh (Cont.)

19	Faridpur	3	3	0	0	19	4	0
20	Rajbari	48	40	13	5	24	22	18
21	Manikganj	70	110	39	27	34	46	40
22	Dhaka	48	5	51	75	66	64	36
23	Munshiganj	0	0	0	0	0	0	0
24	Narayanganj	7	4	6	0	0	0	0
25	Narsingdi	2	0	0	0	0	0	0
26	Gazipur	183	155	200	175	227	195	152
27	Tangail	665	1021	587	680	464	362	339
28	Jamalpur	319	575	430	159	345	153	127
29	Mymensingh	1369	3539	3335	3536	4534	7523	3110
30	Kishoreganj	0	0	0	0	0	0	0
31	Comilla	4	1	0	0	0	0	0
32	Khulna	4	0	0	0	22	37	38
33	Barguna	2	1	4	0	1	0	0
34	Chandpur	0	2	0	0	0	4	0
Total		4283	8110	6113	5920	6892	9379	4932

Source : Kala-azar elimination programme , DGHS

Re-emerging Kala-azar In Bangladesh

The effort was based in large part on indoor residual spraying with DDT. The simultaneous drop in kala-azar incidence was widely seen as a collateral benefit (Birley, 1993). However, within a few years after the end of the eradication effort, kala-azar returned to Bihar and to Bengal on both sides of the border. Investigators hypothesized that patients with Post kala-azar dermal leishmaniasis (PKDL) provided the infection reservoir that initiated foci of resurgence after intensive vector control ended, a hypothesis supported by the demonstration that PKDL patients infected a high proportion of laboratory –reared sand flies fed on them. In Bangladesh, sporadic kala-azar cases were reported in the 1970s, and an outbreak occurred in Pabna district in 1980. There has been kala-azar transmission in Bangladesh every year since then (Elias, Rahman and Khan, 1989). The districts most affected in the early 1980s were reported to have been Sirajganj, Pabna, Mymensinh, Rajshahi and Tangail. From 1994 through 2004, a total of 73,467 kala-azar cases were reported to the Malaria and Vector-Borne Disease Control Unit, Directorate General of Health Services (DGHS), Government of Bangladesh**.** From 1994 to 1996, Pabna district reported the highest annual number of kala-azar cases. After 1996, the incidence in Mymensingh overtook that in Pabna, and has continued to rise since that time. Annual kala-azar incidence rates calculated using total district population as the denominator are misleading, since not all thanas in an affected district report cases. In Mymensingh district, only 5 of 12 thanas reported kala-azar in recent years. Using the population of the respective thana as the denominator, the incidence of kala-azar in Fulbaria thana ranged from 30 to 33/10,000/year since 2000, while that in Trishal, the next most affected thana, ranged from 21 to 26/10,000/year. Over the same period of time,

the incidence in the other 3 endemic thanas, Baluka, Muktagacha, and Goforgaon, ranged from 5 to 15 cases/10,000/year (DGHS 2011).

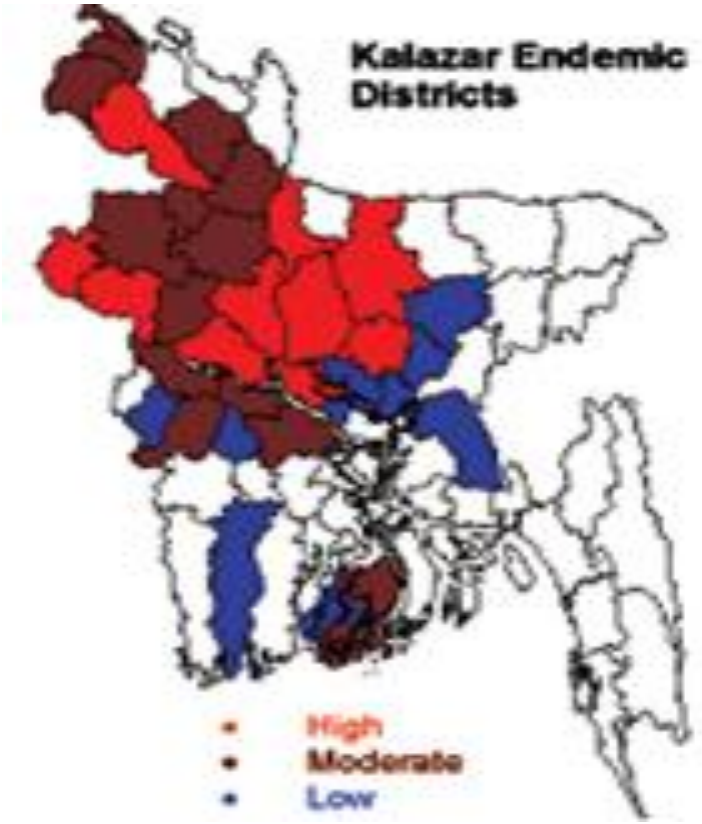

Fig.-4: Cumulative kala-azar cases reported from 1994 to 2004 by district based on national surveillance data. (*Source*: Malaria and Vector-Borne Disease Control Unit, Directorate General of Health Services, Government of Bangladesh, Dhaka)

Aetiological Agent

Leishmaniasis is caused by different species of Leishmania. It is an obligate intra-macrophage protozoa. Leishmania is one of the several genera within the family Trypanosomatidae, and are characterized by the possession of a kinetoplast, a unique form of mitochondrial DNA .A total of about 21 Leishmania species have been identified to be pathogenic to human (Singh, 2006). Leishmania species are widespread in the Old world (Africa, Asia and Europe) and new world (South America and Central America). Visceral leishmaniasis or kala-azar is a systemic disease caused by species of *L. donovani* complex that consists mainly of *L. (d) infantum*, *L. (d) donovani* and *L. (d) chagasi* On the Indian subcontinent (India, Nepal, and Bangladesh) and East Africa the disease is caused by L. donovani and affects both adult and children. *L. infantum* is responsible for VL in children of the Mediterranean basin, Central and West Asia. *L. chagasi* causes VL in children in Latin America, where lymphadenopathy is a dominant clinical feature. There are two types of VL, which differ in their transmission characteristics: zoonotic VL is transmitted from animal to vector to human and anthroponotic VL is transmitted from human to vector to human. In the former, humans are occasional host and animals, mainly dogs, are the reservoir of the

parasite. Zoonotic VL is found in areas of *L. infantum* transmission whereas anthroponotic VL is found in areas of *L. donovani* transmission.

Vector

The insect vector of leishmaniasis, the phlebotomine sand fly, is found throughout the world's inter-tropical and temperate regions. Of 500 known phlebotomine species, only some 30 of them have been positively identified as vectors of the disease (WHO, 2009).The female sand fly lays its eggs in the burrows of certain rodents, in the bark of old trees, in ruined buildings, in cracks in house walls, in animal shelters and in household rubbish, as it is in such environments that the larva will find the organic matter, heat and humidity which are necessary for their development. In its search for blood (usually in the evening and at night), the female sand fly covers a radius of a few to several hundred meters around its habitat (WHO, 2009). Sand fly blood meal analysis in India confirms that Phlebotomus argentipes feed predominantly on bovines, with humans as their second choice. The proximity of cattle may diminish disease transmission by enabling sand flies to feed preferentially on animals not susceptible to leishmaniasis, thereby decreasing sand fly parasite acquisition, feeding on humans, or both (Bern et al., 2005).

Clinical Forms of Leishmaniasis

The three distinct forms, cutaneous leishmaniasis (CL), visceral leishmaniasis (VL), and mucocutaneous leishmaniasis (MCL) are classically caused by a spectrum of different Leishmania species each. Even though there is a clear correlation between the causative species and the clinical presentation, many variations are seen. Depending on the specific characteristics of species /strains and also on the immunocompetence of the host the clinical manifestation may vary to a greater extent. Species causing typically CL may visceralize and visceral species may show dermatotropism. In many endemic areas of the world a few Leishmania species are prevalent simultaneously so that a species specific diagnosis can not rely on clinical findings alone. Species specific diagnosis is necessary for adequate treatment. The type of disease expressed depends both on the type of Leishmania species and on the zymodeme (eletrophoretic isoenzyme pattern) expressed on that species. Thus, one zymodeme may cause visceral leishmaniasis whereas another zymodeme of the same species may cause cutaneous leishmaniasis.

Visceral Leishmaniasis or Kala-Azar

Kala-azar is a disease that is insidious in origin, slow in development, and fearful in effects. Kala-azar is nearly always fatal if untreated (Desjeux, 1996). Even with treatment, case-fatality rates often exceed 10% in VL- endemic areas of Asia and Africa (Berman, 1997). It is typically caused by the Leishmania donovani complex, which includes three species: L. donovani, *Leishmania infantum*, and *Leishmania chagasi*. The clinical features of VL caused by different species are different, and each parasite has a unique epidemiological pattern. On the the Indian subcontinent, the disease is almost exclusively caused by L. donovani. L. infantum is responsible for VL in children in the Mediterranean basin. *L. chagasi* causes VL in children in Latin America, where lymphadenopathy is a dominant clinical feature. *L. tropica*, the causative organism of Old World cutaneous leishmaniasis, is reported to produce visceral disease in non-immune persons. Similarly, visceralization by Leishmania amazonensis, has also been reported. Kala-azar occurs either in a typical zoonotic or an anthroponotic pattern, depending on the species involved. L. donovani depends on inter-

human transmission (Thakur 2000). The clinical presentation of VL is similar in the various endemic areas but there are some differences. For example, enlarged lymph nodes are rarely found in Indian VL patients but are frequent in Sudanese VL patients (Siddig et al., 1990; Zijlstra et al., 1991). Sub clinical infections are thought to exist at such a high number that this alone would be sufficient to maintain the infectious cycle. Besides, PKDL patients are suspected as serving as a reservoir, especially bridging long-term intervals between epidemics. The incubation period varies from 3 to 8 months (range from 10 days to 34 months). Symptoms include fever, weight loss, hepatosplenomegaly (usually spleen much larger than the liver), lymphadenopathy, pancytopenia and hypergammaglobulinaemia. Skin pigmentation may be a feature (kala azar: black disease). It may be asymptomatic and self-resolving but usually runs a chronic course and may be fatal without treatment, or despite treatment. Death usually occurs because of severe secondary bacterial infections in advanced disease. Some cases of visceral leishmaniasis present atypically and cases have been reported that affect the lungs, pleura, oral mucosa, larynx, esophagus, stomach, small intestine, skin and bone marrow.

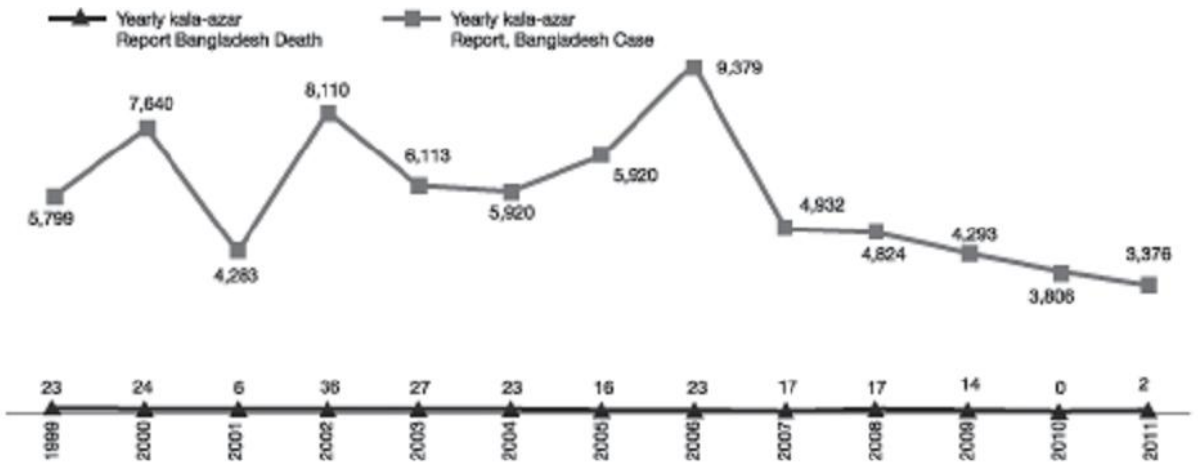

Figure: Morbidity and Mortality of Kala-azar from Year 1999 to 2011 (Health Bulletin 2012)

Clinical Variations of Visceral Leishmaniasis

Post-kala azar dermal leishmaniasis (PKDL) develops after resolution of visceral leishmaniasis. In India, it manifests in 5-15 percent of VL cases after months or several years of remission from infection, while in Sudan, it develops within weeks or months in 50-60 percent of cured VL cases (Zijlstra and El-Hassan, 2001). The disease develops in a variety of clinical forms from hypo pigmented macules to infiltrated papules or nodules. The three major representation of skin lesion are described of which one or two forms predominate and two forms generally co–exist in the same patient. I) Erythematous indurated lesions having butterfly distribution on the face; ii) multiple symmetrical hypopigmented macules with irregular margins that may coalesce, having generalized distribution to the extremities and trunk; and (iii) combination of papules, nodules and plaques. High interleukin-10 (IL-10) levels in the skin and peripheral blood as well as high level of C reactive protein in plasma of patients with VL are predictive of subsequent development of PKDL. In Indian subcontinent, untreated case of VL and PKDL are considered to be the sole reservoir to harbour and disseminate the causative parasite in the absence of zoonotic transmission.

Pathogenesis of VL

The lifecycle of *L. donovani* has two distinct forms like a promastigote flagellar form found in the gut of the arthropod vector and an amastigote form, which develops intracellularly in the mammalian host. Only female phlebotomine sand flies transmit the disease, by inoculation of the promastigote form along with the sandfly saliva which potentiates parasite infectivity into the skin. The parasites are internalized by dendritic cells and macrophages in the dermis and transform into amastigotes by losing their flagella. They multiply and survive in phagolysosomes through a complex parasite–host interaction. Leishmania amastigotes are the only protozoan parasites that survive and reproduce in macrophage phagolysosome which have a p^H of 4.5. Amastigotes are protected from the intravacuolar acid by a proton-transporting ATPase, which maintains the intracellular parasite p^H at 6.5 (Contran et al., 1994**).** The parasites disseminate through the lymphatic and vascular systems and infect other monocytes and macrophages in the reticulo-endothelial system, resulting in infiltration of the bone marrow, hepatosplenomegaly and sometimes lymphadenopathy. Importantly, infection does not always equate with clinical illness. The host specific cell-mediated immune (CMI) response has an important role in controlling the infection. In VL patients, the inability to control L. donovani infection is associated with a profound T-cell unresponsiveness to L. donovani antigens and the production of interleukin 10. IL10-producing $CD25^-Foxp3^-$T cells were recently implicated in the pathogenesis of human VL in India (Nylen et al., 2007). The crucial role of the CMI response is illustrated by the increased risk of developing clinical illness in cases of malnutrition or concomitant immunosuppressive diseases, such as HIV infection. Other risk factors for developing clinical illness have been identified and include young age (Zijlstra et al., 1994), decreased production of interferon γ (IFN-γ) (Carvalho et al.,1992) and polymorphisms in the promoter of the tumour necrosis factor α (TNF-α) gene (Karplus et al., 2002).

Conclusion

Kala-azar is still very alarming in this country. Proper surveillance, complete treatment course and rapid diagnosis is very urgent for elimination of this disease from Bangladesh. Government as well as NGOs should take step jointly overcome this burden.

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