

Pediatric visceral leishmaniasis in northwest of Iran

Babak Abdinia, MD^{a,c,*}, Mohammad Oliaei-Motlagh, MD^b, Amir Teimouri-Dereshki, MD^b

Abstract

Leishmaniasis is one of the major health problems in Iran. Although the incidence of visceral leishmaniasis (VL) is reported almost everywhere, the northwestern Iran is one of the major endemic regions.

To do this study, clinical, laboratory as well as disease characteristics of children admitted to Children Cure and Health Hospital, Tabriz University of Medical Sciences, were examined as the reference hospital for the treatment of VL in northwestern Iran.

In this study, 156 children hospitalized in a pediatric hospital from 2000 to 2015 for VL were included. Gender, age, anemia, thrombocytopenia, increase in the erythrocyte sedimentation rate (ESR), alanine transaminase (SGPT), and aspartate transaminase (SGOT), major clinical manifestations such as fever, splenomegaly, hepatomegaly, treatment type, and the disease were studied.

Among 156 patients examined in this study, 88 (56.41%) and 68 (43.59%) participants were male and female, respectively. The minimum and maximum ages of the infection were 4.5 months and 6 years, respectively. The mean age of the infected children was 17.94 months. Fever (94.24%) and splenomegaly (86.53%) were the most common symptoms of this disease among children. In addition, 49 (31.41%), 64 (41.02%), 18 (11.53%), 33 (21.15%), and 40 (25.64%) participants had leukopenia, hemoglobin count below 8, ESR above 100, ESR above 60, and platelets below 100,000, respectively. Moreover, 39 (25%) and 17 (10.89%) patients had high aspartate transaminase (AST) and alanine transaminase (ALT). Also, 96.2% of the participants responded to the treatment with glucantime. The rate of mortality in this study was 3.2%.

Clinically, almost all children had fever and splenomegaly at the onset of the disease. In addition, hepatic involvement was observed in all cases of mortality, cases with a lack of initial response, and those in need of auxiliary medication. Hepatic involvement appears to be related to the prognosis of the disease. In our study, bone marrow aspiration (BMA) and positive direct antiglobulin test (DAT) were observed in 66.67% and more than 90% of the patients, respectively.

Children with VL in northwestern Iran responded well to glucantime. In case of resistance, amphotericin B was a good alternative. Early diagnosis is essential in reducing mortality rate.

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, BMA = bone marrow aspiration, DAT = direct antiglobulin test, ESR = erythrocyte sedimentation rate, VL = visceral leishmaniasis.

Keywords: anemia, fever, leishmaniasis, pediatric

1. Introduction

Leishmaniasis is a major health problem in Iran.^[1] Kala-azar is a parasitic infectious disease that is caused by a protozoan of the genus *leishmania*. It is a zoonotic disease in that it can be transmitted between animals and humans.^[2]

Leishmaniasis covers a wide spectrum of diseases from cutaneous lesions to fatal visceral leishmaniasis (VL), caused by various species of *leishmania* parasite.^[3] The clinical

manifestation of the disease has 3 forms, namely cutaneous, mucocutaneous, and visceral.^[4]

VL (kala-azar) is caused by different species of *leishmania* such as *donovani*, *Chagas*, and *infantum*, each with a certain geographical distribution.^[5,6] This disease is spread by the bite of infected sandflies, with a body length of 2 to 3 mm, that feed from humans and animals. The reservoirs of this disease, which is transmitted by different species of sandflies, include dogs and canines (fox and jackal).^[7] Transmission through the bite of an infected rodent, organ transplant, accidental inoculation among laboratory staff, congenital transmission, and blood transfusion are among rare cases.^[8,9] The incubation period of the visceral type lasts from several weeks to several months, and sometimes a year. This disease is associated with a wide spectrum of symptoms, from asymptomatic to acute and fatal. The major cause of VL in the Mediterranean, Central Asia, and Iran is *Leishmania infantum*.^[10] Acute leishmania is the most common type of *leishmania* among children, specifically children aged 2 months to 2 years.^[11] The incubation period of the disease lasts from several weeks to several months. Diagnosis of VL in infancy may be delayed due to the long incubation period and nonspecific initial symptoms.^[12] The symptoms of the disease are usually diagnosed with irregular fevers, spleen pain, weight loss, anemia, enlarged liver and spleen, swollen hands and legs, and other nonspecific signs.^[13] Due to the weakened immune system, patients become more prone to other infections.^[14] Although VL has been reported in all regions, the northwestern Iran is one of

Editor: Chia-Kwung Fan.

The authors have no funding and conflicts of interest to disclose.

^a Department of Pediatrics, Faculty of Medicine, ^b Faculty of Medicine, ^c Medical Education Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

* Correspondence: Babak Abdinia, Department of Pediatrics, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz 5136735886, Iran (e-mail: babdinia@yahoo.com).

Copyright © 2016 the Author(s). Published by Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

Medicine (2016) 95:44(e5261)

Received: 19 April 2016 / Received in final form: 30 September 2016 /

Accepted: 30 September 2016

<http://dx.doi.org/10.1097/MD.0000000000005261>

the major endemic regions. The early diagnosis is very important, as the disease is completely curable with timely treatment. Given the importance of this disease in Northwest Iran province, the retrospective study to determine the clinical manifestations and demographic characteristics of the patients was performed.

2. Methodology

To do this retrospective study, clinical, laboratory as well as disease characteristics of children admitted to Children Hospital, Tabriz University of Medical Sciences were examined as the reference hospital for the treatment of VL in northwestern Iran. All records of patients diagnosed with leishmaniasis during these years were admitted by one of the authors of the study were extracted from the archives of the hospital. In this study, 156 children hospitalized in the pediatric hospital from 2000 to 2015 for VL were included. Diagnosis criteria were the observation of amastigotes in bone marrow smear and/or positive direct agglutination test (DAT) results. Patients who merely received treatment for clinical leishman were excluded from the study. The place of living, gender, age, anemia, thrombocytopenia, increase in erythrocyte sedimentation rate (ESR), alanine transaminase (SGPT), and aspartate transaminase (SGOT), major clinical manifestations such as fever, splenomegaly, hepatomegaly, treatment type, and finally the disease were studied. All obtained data were analyzed. To use the data from this study, all parents have been allowed and signed informed consent.

3. Results

3.1. Epidemiological specifications

Among 156 patients examined in this study, 88 (56.41%) and 68 (43.59%) participants were male and female, respectively. The minimum and maximum ages of the infection were 4.5 months and 6 years, respectively. The mean age of the infected children was 17.94 months. Except 2 Azerbaijani children, the remaining patients lived in the northwest region of Iran. It is worth noting that the prevalence of this problem is high in certain cities, in particular the northwestern Iran.

3.2. Clinical and laboratory symptoms

Fever was the most common symptom among the children (94.24%). According to clinical examinations, 135 children had splenomegaly. In addition, all children (100%) had enlarged spleen in ultrasonography. Examinations showed a 51.28% prevalence for enlarged liver. In addition, liver ultrasound showed that the liver size in 62.17% of patients was larger than normal. In addition, no case with lymphadenopathy was observed. According to the laboratory results, 49 (31.41%) children had leukopenia, 64 (41.02%) had hemoglobin below 8 g/dL, 21 (13.46%) had hemoglobin between 8 and 10 g/dL, 18 (11.53%) had ESR above 100, 33 (21.15%) had ESR above 60, 40 (25.64%) had platelet below 100,000, and 25 (16.02) had platelet level of 100,000 to 150,000. (Table 1) Moreover,

Table 1

Main signs of children with kala-azar.

Signs	Fever	Splenomegaly	Hepatomegaly	Petechiae and purpura
No. of patients (%)	92.4	86.53	51.28	11.53

39 (25%) children had high AST and 17 (10.89%) had high ALT. In 10 cases (6.41%), negative DAT and in 55 cases (33.33%) negative bone marrow aspiration (BMA) were observed (Table 2).

3.3. Treatment and prognosis

In all cases, 28-day course of intramuscular injection of glucantime was the medication of choice and the front line of treatment. Due to the lack of clinical response, amphotericin B and allopurinol were administered as auxiliary medications in 6 (3.8%) and 1 (0.64%) cases, respectively. In addition, no case of recurrence was reported. In terms of prognosis, there were 5 (3.2%) cases of mortality. In other cases, complete remission was observed. Follow-up studies reported the improvement of symptoms and no case with cutaneous involvement.

4. Discussion

Leishmaniasis is an endemic problem in some northwest regions of Iran. However, new cases of this disease have been currently reported in regions not categorized as endemic or nonendemic. In the current study, the majority of patients were younger than 2 years old. Epidemiologically, VL has been often observed in children younger than 10 years of age.^[15] In a study (1985–1990), 90% of patients were younger than 5 years of age.^[16] According to a study in the Fars Province by Edrissian et al,^[17] only 6% of the patients were older than 4 years of age. In this study, the majority of the hospitalized leishmania patients were younger than 2 years (with the mean age of 17 months). In a study by Grech et al^[18] in Malta (1981–1998), 81 cases with leishmania were among children aged 34 months on average. In a study by Cascio in Sicily (1980–2000), the mean age of the patients was reported as 1.7 years.^[19] In the current study, the minimum age of infection was 4.5 months. It seems that the prolongation of the incubation period, acquired immune transmission from mother to child in endemic regions, and covering up children (which reduces the chance of child-mosquito contact play a part in rare observation of this disease among children younger than 6 months.

Clinically, almost all children had fever and splenomegaly at the onset of the disease. This finding is consistent with the findings of previous studies conducted in this region and other regions in Iran. Fever and splenomegaly were observed in 100% of cases in Turkey and 95% of cases in southern Greece.^[20,21] The prevalence of fever and splenomegaly was 95% and 100% in the south of France, respectively.^[22] In this study, lymphadenopathy was not among clinical symptoms. Although its prevalence was

Table 2

Hematologic features of children with kala-azar.

Laboratory	No. of patients (%)
Anemia < 8 g/dL	13.46
Leucopenia	41.02
100 > ESR > 60	25.64
ESR > 100	21.15
High AST	25
High ALT	10.89
Negative DAT	6.41
Negative BMA	33.33

ALT = alanine transaminase, AST = aspartate transaminase, BMA = bone marrow aspiration, DAT = direct antiglobulin test, ESR = erythrocyte sedimentation rate.

reported to be 3% by another study, lymphadenopathy was not among the clinical symptoms in the south of Iran.^[23] In previous studies, the lymph node metastasis was not reported in this area. In a study conducted in Malta, only a 4% prevalence rate was reported for lymphadenopathy.^[16] Liver is an involved part in this study that may be associated with an increase in liver enzymes. In our study, about half of the patients had hepatomegaly, but the majority of them were not associated with an increase in liver enzymes. Liver involvement has been observed in all cases of mortality, cases with a lack of initial response, and those in need of auxiliary medication. Although liver involvement can be associated with the prognosis of the disease, this claim requires further investigations. Complete remission and normalization of liver enzymes have been observed in other cases. In a study in Saudi Arabia, hepatitis and disseminated intravascular coagulation (DIC) were among the factors associated with bad prognosis. In another study in this country, the prevalence of hepatomegaly was reported as 1.0%.^[24,25] Hemotologically, anemia was a prevalent problem. According to laboratory symptoms, pancytopenia and high inflammatory markers were common findings, in such a way that more than half of children had anemia below 10 and all children had high ESR (one-third of the cases had over-60 ESR). A very high ESR has been sometimes caused by concurrent secondary infection.^[26] Studies have reported 10% to 26% prevalence of the secondary infection. Diagnosis of leishmaniasis has been simplified with an emphasis on and attention to clinical symptoms, living in or traveling to endemic areas, and the use of specialized methods. In VL, the observation of amastigotes in the biopsy or aspirate obtained from visceral organs, including spleen, liver, lymph nodes, and bone marrow, is the definitive diagnostic procedure. The sensitivity of parasitological techniques, such as bone marrow puncture, microscopic observation, and parasites analysis, has been estimated up to 98% for spleen, 45% to 86% for bone marrow, 60% for liver, and 64% for lymph nodes.^[27,28] Although leishmania parasites are usually observed in spleen of infected patients, sampling from this organ is rarely done due to the risk of bleeding spleen; instead, bone marrow puncture is more frequently exercised in children. Although the diagnosis of kala-azar is confirmed with the observation of leishman bodies in parasitological techniques, failure in detection of parasite necessitates the use of auxiliary serological methods. This is because their sensitivity depends on the sampling technique and the experience of sample collector. Studies in Iran have estimated the sensitivity of this method from 35% to 63%. In our study, the BMA was positive in 66.67% of cases, which is consistent with other studies. In addition, the DAT for serologic diagnosis is more common in Iran. This method is superior to other normal methods in terms of simplicity, cost-effectiveness, and validity (sensitivity and specificity). In our study, DAT was positive in more than 90% of cases. Sinha and Sehgal^[28] reported a near 95% sensitivity for DAT. Results from the present study showed that, although enzyme-linked immunosorbent assay (ELISA) and immunofluorescent antibody assay (IFA) are well efficient in the diagnosis of patients with kala-azar, their implementation requires an equipped laboratory and skilled personnel. On the contrary, DAT is a simple and inexpensive method for VL diagnosis and seroepidemiologic studies, as it does not require complicated equipment and is applicable in endemic regions. As a result, it can be a suitable alternative for costly methods such as ELISA and IFAT. Timely treatment plays an important role in the prevention of mortality. The normal treatment in Iran is the use of pentavalent antimony (glucantime)

as the front line of treatment. In our study, 96.2% of the participants responded to glucantime.^[29-31] In some regions such as India, where amphotericin B is the front line of treatment, glucantime resistance of 20% to 50% has been reported. The rate of mortality in our study was 3.2%. This rate has been reported as 5% and 2% in the studies by Haidar et al^[32] and Lita et al,^[26] respectively. Limitations of our study include that this is a retrospective study and it is possible that the information was incomplete and the fact that we could not all prove clinical resistant to glucantime through laboratory.

5. Conclusion

Children with VL in northwestern Iran respond well to glucantime. In case of resistance, amphotericin B is an acceptable alternative. Early diagnosis is essential in reducing mortality rate. It is also required that physicians in endemic regions have adequate knowledge of the disease.

References

- [1] Mohebbali M, Javadian E, Yaghoobi-Ershadi MR, et al. Characterization of Leishmania infection in rodents from endemic areas of the Islamic Republic of Iran. *East Mediterr Health J* 2004;10:591-9.
- [2] Darchen Kora NN, Dergachera TL. Patterns in the distribution of visceral leishmaniasis in transcaucasia. *Med Parasitol Mosk* 1989;4: 28-37.
- [3] Alvar J, Vélez ID, Bern C, et al. Leishmaniasis worldwide and global estimates of its incidence. *PLoS One* 2012;7:e35671.
- [4] Ashford RW, Desjeux P, De Readt P. Estimation of population at risk of infection and number of cases of leishmaniasis. *Parasitol Today* 1992;8:104-5.
- [5] Rab MA, Evans DA. Leishmania infantum in the Himalayas. *Trans R Soc Trop Med Hyg* 1995;89:27-32.
- [6] Cabello PH, Lima AM, Azevedo ES, et al. Familial aggregation of Leishmania chagasi infection in northeastern Brazil. *Am J Trop Med Hyg* 1995;52:364-5.
- [7] Rassi Y, Azizi K, Motazedian MH, et al. The seminested PCR based detection of leishmania infantum infection in asymptomatic dogs in a new endemic focus of visceral leishmaniasis in Iran. *Iran J Arthropod Borne Dis* 2007;1:38-42.
- [8] Mansueto P, Seidita A, Vitale G, et al. Transfusion transmitted leishmaniasis. What to do with blood donors from endemic areas? *Travel Med Infect Dis* 2014;12(6 Pt A):617-27.
- [9] Pereira CM, Oliveira HM, Lopes V, et al. Visceral leishmaniasis after orthotopic liver transplantation: a rare cause of infection. *Transpl Infect Dis* 2016;18:251-4.
- [10] Alborzi A, Rasouli M, Shamsizadeh A. Leishmania tropica-isolated patient with visceral leishmaniasis in southern Iran. *Am J Trop Med Hyg* 2006;74:306-7.
- [11] Rocha NA, Silva GB, Oliveira MJ, et al. Visceral leishmaniasis in children: a cohort of 120 patients in a metropolitan city of Brazil. *Turk J Pediatr* 2011;53:154-60.
- [12] Petrela R, Kuneshka L, Foto E, et al. Pediatric visceral leishmaniasis in Albania: a retrospective analysis of 1,210 consecutive hospitalized patients (1995-2009). *PLoS Negl Trop Dis* 2010;4:pii: e814.
- [13] Gupta V, Tripathi S, Tilak V, et al. A study of clinico-haematological profiles of pancytopenia in children. *Trop Doct* 2008;38:241-3.
- [14] Alexandropoulou O, Tsolia M, Kossiva L, et al. Visceral leishmaniasis: a common cause of post-infectious febrile pancytopenia in children in an endemic area: experience of a children's tertiary hospital. *Pediatr Emerg Care* 2012;28:533-7.
- [15] Nadim A, Navid-Hamidid A, Javadian E, et al. Present status of kala-azar in Iran. *Am J Trop Med Hyg* 1978;27(1 Pt 1):25-8.
- [16] Soleimanzadeh G, Edrissian GH, Movahhed-Danesh AM, et al. Epidemiological aspects of kala-azar in Meshkin-Shahr, Iran: human infection. *Bull World Health Organ* 1993;71:759-62.
- [17] Edrissian H, Nadim A, Alborzi AV, et al. Visceral leishmaniasis: the Iranian experiences. *Arch Iranian Med* 1998;1:22-6.
- [18] Grech V, Mizzi J, Mangion M, et al. Visceral leishmaniasis in Malta: an 18 year pediatric, population based study. *Arch Dis Child* 2000; 82:381-5.

- [19] Cascio A, Colomba C, Antinori S, et al. Pediatric visceral leishmaniasis in Western Sicily, Italy: a retrospective analysis of 111 cases. *Eur J Clin Microbiol Infect Dis* 2002;21:277–82.
- [20] Totan M, Dagdemir A, Muslu A, et al. Visceral childhood leishmaniasis in Turkey. *Acta Paediatr* 2002;91:624.
- [21] Maltezou HC, Sifas C, Mavrikou M, et al. Visceral leishmaniasis during childhood in southern Greece. *Clin Infect Dis* 2000;31:1139–43.
- [22] Minodier P, Garnier JM. Childhood visceral leishman in provence. *Archpediatr* 2000;7(suppl 3):572s–7s.
- [23] Kadivar MR, Kajbaf TZ, Karimi A, et al. Childhood visceral leishmaniasis complicated by bacterial infections. *East Meditter Health J* 2000;6:879–83.
- [24] Al-juroyyan NA, Al-Nasser MN, Al-Fawaz IM, et al. The haematological manifestations of visceral leishmaniasis in infancy and childhood. *J Trop pediatr* 1995;41:143–8.
- [25] Benjamin B, Annobil SH, Bassuni WA. Diagnostic and management problems in childhood visceral leishmaniasis in southwestern Saudi Arabia. *Ann Trop pediatr* 1994;14:7–13.
- [26] Lita G, Davachi F, Sulcebe G, et al. Pediatric visceral leishmaniasis in Albania. *Int J Infect Dis* 2002;6:66–8.
- [27] Herwaldt BL. Leshmaniasis. *Lancet* 1999;354:1191–8.
- [28] Sinha R, Sehgal S. Comparative evaluation of serological tests in Indian kala-azar. *J Trop Med Hyg* 1994;97:333–40.
- [29] Minodier P, Piarroux R, Garnier JM, et al. Pediatric visceral leishmaniasis in southern France. *Pediatr Infect Dis J* 1998;17:701–4.
- [30] Berman J. Chemotherapy of leishmaniasis: recent advances in the treatment of visceral disease. *Curr Opin Infect Dis* 1998;11:707–10.
- [31] Jebbari H, Davidson R. Recent advances in leishmaniasis. *Curr Opin Infect Dis* 1998;11:535–9.
- [32] Haidar NA, Diab AB, El-Sheik AM. Visceral leishmaniasis in children in the Yemen. *Saudi Med J* 2001;22:516–9.