Clinical findings and initial treatment response of patients with visceral Leishmaniasis admitted in Ali asghar children hospital from 1976 to 2010 in Tehran, Iran

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Abstract

Background: Visceral Leishmaniasis (VL) is a spreading potentially fatal zoonosis in Iran mimicking many other diseases in infancy which differs from VL in some other regions in terms of it’s clinical characteristics and response to therapy; earlier and better management is quite effective for life saving.

Patients and Methods: All cases with final diagnosis of VL, 2 months to 12 years who were discharged from Ali Asghar children hospital from 1976 to 2010 were enrolled in this descriptive-analytic retrospective study; demographic, clinical, paraclinical parameters as well data concerning initial response to treatment were gathered and analyzed by appropriate statistical methods by SPSS software.

Results: 58 patients with final diagnosis of Kala azar were admitted in Ali asghar children hospital from 1976 to 2010. 36 cases (62%) were male; mean age of patients was 30 months (SD=24.98); Most cases had been admitted in spring (21cases, 36%) and winter (18 cases, 31%), 43% were living in Tehran and around Tehran. Fever was the most common symptom and observed in 54 cases (93.1%) followed by splenomegaly, hepatomegaly, pallor and cough. There was a significant association between fever onset until admission and presence of splenomegaly (P value=0.015), weight loss (P value=0.025) and pallor (0.029). Most cases (93%) had been treated by Glucantime; mostly with doses less than 20 mg/kg/day and there was no significant difference regarding initial response (stopping fever) between those who got final dosages less than or equal to 20 mg/kg/day and those who received higher doses.

Conclusion: Comparing to previous studies, there were some differences concerning presenting symptoms and signs on admission probably due to late diagnosis of VL in recently infected areas. Glucantime still has good effect for VL in Iran and it's lower doses might also be effective for treatment although follow up studies are needed.

Keywords: Kala azar, children, Iran, Leishmania infantum

Introduction

Visceral Leishmaniasis (Kala Azar; VL) is a zoonosis which is caused mainly by L. donovani complex but also by other species of Leishmania like L. infantum (in Mediterranean region including Iran) and L. tropica (recently in middle east) and L. amazonensis in Latin America. VL is found in a broad belt that extends from the Strait of Gibraltar across the Mediterranean through Asia to the east coast of China (1). Even recent studies in Iran has shown high rate of infectivity and transmission; for example a new survey in Azarshahr located in northwest part of country showed that by direct agglutination test there is 1.3 % positivity for collected specimens with \( \geq 13200 \) titters and 2.2% with 1:1600 titters suspicious (2).

Transmission is by various species of sandfly; in Mediterranean type of VL, usually infants are affected; Controlling the disease is so difficult as there are many canine reservoirs like foxes and dogs (3). The incubation period varies from 6 weeks up to 10 years (1); so taking the history of travel to contaminated regions in Iran might be difficult. As the disease has been spreading all over the country and first symptoms and signs specially in infancy are nonspecific and without treatment the course is usually fatal, knowledge about it’s clinical symptoms and signs as well as paraclinical features for all physicians in countries with enzootic situation is critical. On the other hand, various drug regimens and dosages have been suggested for various types of Leishmanias and recently Antimony resistance have become a major problems in some countries (1,4,5), so looking to primary response to conventional treatment in our referral centers is also important. In Iran there are some studies from centers with various climate and geographical regions which has had various results and also some similarities; in northwest region (Ardebil) (6,7), southern parts like Kerman (8), western parts like Yasooj (9), and also children medical center in Tehran (10); last one is relatively old study, so we tried to look at our cases from demographic, clinical and also initial response to therapy in a tertiary, educational center in Tehran, Iran.

Patients and methods

All cases with final diagnosis of VL, 2 months to 12 years who were discharged from Ali Asghar children hospital from 1976 to 2010 were enrolled in this descriptive-analytic retrospective study. Patients were diagnosed as VL if they had compatible clinical findings with positive
serology (IFA titer higher than 1:128), positive tissue smear for Leishman bodies or both. Ali Asghar children hospital is a tertiary children hospital in Tehran. A questionnaire including demographic, clinical, paraclinical parameters as well data concerning initial response to treatment were gathered; all data were transferred to SPSS software (version 16) and appropriate statistical tests including Chi square tests for qualitative parameters and Student t-test for continuous parameters were used for statistical analysis; P value equal or less than 0.05 were considered significant. Ethical issues were considered as the study was approved by ethical committee of Medical college of Tehran University of medical sciences and all articles of declaration of Helsinki including respecting the patients, keeping secret the patients names and not doing a direct intervention were respected during the study.

Results
58 patients with final diagnosis of Kala azar were admitted in Ali asghar children hospital from 1976 to 2010. 36 cases (62%) were male; mean age of patients was 30 months (SD=24.98) and age range was from 4 months to 120 months; most cases were toddlers (12-24 months of age; 22 cases, 37.9%) and infants (less than 12 months of age; 14 cases, 24.1%); overall 62% of patients were less than 24 months of age. Most patients (43%) were living in Tehran and around Tehran; there was a history of travel to known contaminated regions just in 10% of them. 34.5% of cases came from Northern and Northern west part of country and remainder were living in other parts of Iran. Most cases had been admitted in spring (21 cases, 36%) and winter (18 cases, 31%).

From clinical point of view, fever was the most common symptom and observed in 54 cases (93.1%); Mean duration of fever before admission was 62 days (SD=76.29 days). Other frequent symptoms and signs and main paraclinical findings were shown in table 1. Underlying disorders were found in 3 cases (two cases of vesicoureteral reflux and one case of epilepsy).

4 cases were presented with complains other than fever from which 3 cases had presented with abdominal distension and pallor and one cases had been referred as a resistant relapsing picture of Kala azar to our center.

There was a significant association between fever onset until admission and presence of splenomegaly (P value = 0.015), weight loss (P value = 0.025) and pallor (0.029); so the more protracted course of fever, the more occurrence of splenomegaly, pallor and weight loss on admission.

When age groups (less than 12 months, 1-2 years, 2-3 years, above 3 years) were checked for frequency of symptoms and signs of diseases on admission, we found a significant relationship also between age groups and cough (P value = 0.029); so cough was more common in infants on admission.

For diagnosis purpose, Immunofluorescence antibody (IFA) test had been requested just for 34 cases; all of them had positive results (at least 1:128); however, in 16 cases (27%) it was the only diagnostic test. 31% (18 cases) were diagnosed just by positive findings in bone marrow aspirates (BMA) and both tests had been requested for 18 cases (31%) of which IFA was positive in all of them but BMA was positive in just 6 cases. 6 cases (10%) have been referred from other centers and their primary diagnostic tool was not known.

Blood culture was requested from 52 cases from which, 3 cases (5.2%) the results were positive; Urine cultures which were requested from 51 cases had a positivity rate of 32.8% (19 cases); so significant number of cases showed concurrent bacterial infections.

Mean duration of admission on hospital was 15 days (SD = 9.16 days); overall, duration of admission was less than 15 days in 60% of patients.

Concerning treatment modalities, 54 cases were started with Glucantime (93.1%) and was used on daily basis; Mean dosage for Glucantime was 24 mg/kg/day (SD = 12.7). Mean duration of Glucantime usage at hospital was 11.2 days (SD = 5.6 days). 4 cases were treated initially with Amphotericin B deoxycolate (one case with adjunctive Gamma interferon); these four cases were those whose previous treatment in other centers with Glucantime was unsuccessful.

Table 2 shows the dosages, duration of administration and

<table>
<thead>
<tr>
<th>Clinical findings on admission</th>
<th>Fever</th>
<th>Splenomegaly</th>
<th>Hepatomegaly</th>
<th>Pallor</th>
<th>Cough</th>
<th>Weight loss</th>
<th>Diarrhea</th>
<th>Generalized lymphadenopathy</th>
<th>Petechia</th>
<th>Icter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1. Frequency of main clinical and paraclinical findings in 58 cases of VL in children</td>
<td>93.1%</td>
<td>91.4%</td>
<td>74%</td>
<td>63.8%</td>
<td>29.3%</td>
<td>20.7%</td>
<td>17.2%</td>
<td>12.1%</td>
<td>10.3%</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

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<tr>
<th>Lab findings on admission</th>
<th>Anemia (hemoglobin less than 12 gr/dl)</th>
<th>Mean value of hemoglobin</th>
<th>Thrombocytopenia (platelet less than 150000/mm³)</th>
<th>Leukopenia (WBC less than 4500/mm³)</th>
<th>Mean value of first hour erythrocyte sedimentation rate</th>
</tr>
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changes in drug dosages in patients who took Glucantime. As it has been shown, most patients have been treated with doses less than 20 mg/kg/day (equal to 7 mg/kg of elemental Antimony). Overall, mean duration for diminishing fever in all patients (58 cases) was 5.7 days (SD=6.2 days). For Glucantime group, there was no significant difference regarding initial response(stopping fever) between those who got final dosages less than or equal to 20mg/kg/day(mean duration for response=6.83 days, SD=4.6 days) and those who received higher doses(mean duration for response=6.57 days, SD=3.8 days)(Test calculated P value=0.19).

Regarding discharge, outpatient prescription of Glucantime was used for completion of therapy in 51 cases; 5 cases got their full course of medication and discharged without further drug, one case was discharged with oral Ketoconazole (after AMB+Gamma interferon therapy)(total=57cases). In one case, clinical feathers of hepatic failure, sepsis and multiorgan failure were evident on admission and was expired in spite of receiving AMB and antibiotics.

**Discussion**

First case of VL in Iran was reported in 1939 in Mazandaran province in northern part of Iran; Thereafter numerous cases have been reported; from 1944 to 1986, 5244 cases have been reported with more than half of cases from Ardebil province in north-west part of Iran(3). At present time the disease have been spreading to vast majority regions of country including Central(Markazi) Province with documented cases around Tehran as Iranian Capital city due to difficulties for controlling both vector and reservoirs(3). Various climates can affect that, so there are various results from epidemiological studies in different parts of Iran(3,6,7,8,9,10). As Tehran is situated in a temperate climate, our results from seasonal point of view is similar to children medical center study but different from results in northern and southern studies in Iran(6,7,8,9) as in latter studies most cases have been admitted in the winter; this might be explained by vector reproduction cycle and activity.

Most cases in our study were male and this is in accordance to other Iranian and foreign studies(6,7,8,9,10,11), this has been explained by more outdoor activity of boys (for toddlers) in contaminated regions, different dressing allowing more bites for males and relatively lower activity of immune system in them(4). This stresses on male behavior modifications in these regions specially at the evening hours when sandfly activity is highest(3).

Regarding age, our study has a similar age distribution to other studies in Iran(6,8), as *L.infantum* usually affects infants and toddlers in middle east region(1). These kids are usually unable to protect themselves from sandfly bites; the inherent problem of immune system for phagocytosis in this age group in conjunction to impaired function of reticuloendothelial system (Hepatosplenomegaly) and cellular system(malnutrition) can impose them to various dangerous secondary bacterial infections as we found many cases of urinary tract infection and bacteremias.

Nearly half of cases in this study were living in Central province and minority had a history of travel to other parts of country, this shows that this part of country is increasingly involved and physicians should have VL in mind when facing with compatible clinical pictures.

Mean duration of fever in this study was longer than study in southern part of Iran(8), still it is shorter than previous study in Tehran(10); Probably residence in contaminated regions and more familiarities with disease characteristic by physicians specially general practitioners can help to earlier diagnosis. This again stresses on more practical educational programs for such a zoonoses in more recently affected provinces in Iran. It was shown that splenomegaly, weight loss and pallor were significantly associated with more protracted febrile illness and secondarily may affect the prognosis.

Considering other clinical symptoms and signs, our study showed that most cases had been presented with protracted fever, plenomegaly and hepatomegaly and magnitude of paraclinical parameters like anemia, leukopenia and thrombocytopenia were similar to other Iranian studies (5,6,7,9). As it was shown, the presence of unexplained cough and diarrhea in association with above findings are helpful specially in infancy; On the other hand, icter and lymphadenopathy are uncommon findings in Mediterranean type of VL(1,3).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>results</th>
<th>Total number</th>
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<tbody>
<tr>
<td>Glucantime dosage(mg/kg/day)</td>
<td>-Less than 15:8 cases(15.1%)</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>-15-20:20 cases(37.7%)</td>
<td></td>
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<tr>
<td></td>
<td>-21-40:18(34%)</td>
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<td></td>
<td>-more than 40:8(15.1%)*</td>
<td></td>
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<tr>
<td>Dosage modifications</td>
<td>-reduction: 5 cases(9.3%)</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>-no changes: 2 cases(53.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-increasing: 20 cases(37%)*</td>
<td></td>
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<tr>
<td>Duration of Glucantime administration at hospital</td>
<td>-less than 7 days: 13 cases(24.1%)</td>
<td>54</td>
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<tr>
<td></td>
<td>-8-10 days: 14 cases(25.9%)</td>
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<td></td>
<td>-11-15 days: 15 cases(27.8%)</td>
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<td></td>
<td>-longer than 15 days: 12 cases(22.2%)</td>
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*For 3 cases, allopurinol and gamma interferon had been added due to unresponsiveness.
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There was some limitations for this study:some charts were too old and excluded from the study and this affected the total number of cases and also we didn’t have follow up study for detection of relapses:again a multicentric case control study as a multicentric research could be useful for more exact study of clinical courses with different drug regimen in Mediterranean type of VL.

Acknowledgement
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