Visceral Leishmaniasis in children in the Yemen

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ABSTRACT

Objectives: The clinical presentation and duration of therapy for visceral leishmaniasis varies in different countries. The sodium stibogluconate is costly, and a trial of short course therapy has not yet been studied in Hajjah governorate. The aim of this study was to evaluate the efficacy of a 20 days regimen of sodium stibogluconate and to ascertain the epidemiological, clinical and laboratory features of visceral leishmaniasis in children.

Methods: This was a prospective hospital-based study in Hajjah Governorate, Republic of Yemen. Children of 12 years of age or less with a confirmed diagnosis were included. Sodium stibogluconate was given in a dose of 15mg/kg/dose daily for 20 days, then the patients were re-evaluated and the data required for achieving the other objective was collected.

Results: Thirty-two patients fulfilled the inclusion criteria. The age ranged from 12 months to 144 months (67.7 +/- 35). Females formed 53% of this criteria. The duration of symptoms ranged from 2 weeks to 116 weeks. Fever, fatigability and abdominal distension were the most common symptoms. The hematological findings showed anemia in all patients, leukopenia in 81% and thrombocytopenia in 56%. Formol gel test was negative in 20 patients (63%). Malaria smear was positive in 11 patients (34%). Splenic aspiration was carried out in 25 patients (78%) and bone marrow aspiration in 7 patients (22%). Blood transfusion were required for 24 patients (73%). After 20 days treatment with pentostam, 20 patients (63%) came for follow-up and re-tested for parasitological cure. Half of those were still positive for leishmania donovan bodies. The mortality rate was 5%.

Conclusion: The clinical features were of the Mediterranean type. Twenty days treatment with sodium stibogluconate was not adequate.

Keywords: Visceral leishmaniasis, children.

Saudi Med J 2001; Vol. 22 (6): 516-519

Visceral leishmaniasis is a life threatening disease if not diagnosed and treated early. The disease is known to be endemic in southern Saudi Arabia, which borders with our study area. The disease is transmitted by the sandfly,[2] but solid organ transplantation was reported to be a route of transmission for this disease.[3] Several drugs were used for the treatment of visceral leishmaniasis. The most commonly used drugs were antimonials.[4] Amphoterecin-B was usually reserved for the resistant cases.[5,6] Recently an oral agent (miltefosine) was used.[7] The response to treatment was variable.[8,9] Sodium stibogluconate (SS) was reported to be effective within 15 days when given in combination with aminosidine.[10] A regimen of 15 days of SS was effective in Sudan,[11] and a therapy of 3 weeks duration was effective in the southwest part of Saudi Arabia.[12] On the other hand, a longer duration of therapy for 30 days has been used on more occasions.[11,13-15] In view of these studies, in addition to the fact that the drug is currently given parenterally (harmful route) and expensive especially in a poor population where the disease is endemic our objectives were to study the effectiveness of SS in a dose of 15mg/kg/day for 20 days rather than a longer course of 30 days and to study the epidemiological, clinical and laboratory features.

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Received 30th November 2000. Accepted for publication in final form 17th February 2001.

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Methods. This was a prospective study carried out from January 1999 until June 1999 at the Saudi Hospital, Hajjah, Republic of Yemen. Although it is a 60-bedded hospital, the Ambulatory Care Department is overloaded. The case definition was based on compatible clinical and hematological findings confirmed by positive leishmania donovan bodies in the splenic or bone marrow aspirate. The bone marrow aspirate was carried out when there was contraindication for splenic aspiration. Splenic aspiration was carried out by the technique and precautions described in the World Health Organisation report.[2] The inclusion criteria were: all the confirmed cases of visceral leishmaniasis up to 12 years of age with an agreement from the parents or relatives for follow-up. The relatives were also requested to bring the empty drug container as well as a paper indicating the daily injections of SS. This drug was given in a dose of 15mg/kg/day for 20 days then splenic or bone marrow aspirate was repeated to confirm the parasitological cure in addition to the history of clinical improvement. If the aspirate was still positive for leishmania donovan bodies, the course of SS was continued for 30 days with a plan for further follow up for detecting any possible relapse.

Results. Thirty-two patients fulfilled the inclusion criteria. The age ranged from 12 months to 144 months (67.7 +/- 35), 50% of them were 5 years of age or less and 50% of them above 5 years of age (61-144 months). Females formed 53%. Fever (100%), fatigability (100%), and abdominal distension (91%), were the most common symptoms followed by cough (38%) and epistaxis (16%). The duration of symptoms ranged from 2 weeks to 116 weeks (24.1 +/- 21) but 81% of them had the symptoms from 3 months to 1 year. Pallor, splenomegaly and wasting were found in 100% of the patients, followed by hepatomegaly in 75% and lymphadenopathy in 3%. History of taking antimalarial drugs was positive in 47%. The hematological findings showed anemia in all the patients, leukopenia in 81% and thrombocytopenia in 56% (3% had platelet count below 20,000/cmm) (Table 1). Formal gel test was negative in 20 patients (63%). Malaria smear was positive in 11 patients (34%). Splenic aspiration was carried out in 25 patients (78%) and bone marrow aspiration in 7 patients (22%). Blood transfusion were required for 24 patients (73%). After 20 days treatment with SS, 20 patients (63%) came for follow-up and re-tested for parasitologist cure. Half of them were still positive for leishmania donovan bodies. Based on this result the 2 groups (positive and negative leishmania donovan bodies) were compared by using T-test and chi-square test for age, sex, duration of symptoms, type of symptoms, hematological parameters, formol gel test with no statistically significant difference. The group with positive leishmania contained more patients with negative malaria smear but the p-value did not reach a significant level (0.057). In comparing the negative and positive formol gel test, the only significant association was found between the positive history of abdominal distension and positive formol gel test (p-value = 0.02). The positive malaria smear group was compared to the negative one and the chi-square test showed a significant difference when compared regarding cough, with more cough in the malaria smear positive group (p-value = 0.006) also the blood transfusions were required more with the positive malaria smear group (p-value = 0.002). Among the group who came for follow-up, one patient died after 3 days of initiating the treatment, giving a mortality rate of 5%.

Table 1 - Hematological parameters of patients with visceral leishmaniasis in Hajjah.

Parameter	Groups	No. of Patients	% of Total
WBC (x10^3/cmm)	≤ 2	10	31
	2.1-3	10	31
	3.1-4	6	19
	>4	6	19
	Total	**32**	**100**
Hemoglobin (g/dl)	<5	15	47
	5-7.9	13	41
	8-10.9	4	13
	≥ 11	0	0
	Total	**32**	**100**
Platelets/cmm	<20,000	1	3
	20000-490000	4	13
	50000-149000	13	41
	≥ 150000	14	44
	Total	**32**	**100**

WBC=White blood cell, No=Number

Discussion. A number of 32 pediatric patients with visceral leishmaniasis over a 6 month period in one hospital indicated that this disease is endemic in Hajjah, Republic of Yemen. In our study, both young and older children were equally affected, though in a nearby governorate and in the nearby region of Saudi Arabia the majority were young children.[16,17] There was a minimal predominance of females in our study, in other studies this minimal difference was more in males.[6,17] A significant variation was not expected due to the similar rate of exposure in children regardless of the sex difference. There was a wide range in the duration of symptoms but the majority had their symptoms for more than 3 months which

was similar to a previous report.[18] The delayed presentation to the hospital was attributed to many possible factors; mainly the delay in suspecting the disease by the primary health care physician and attributing the clinical manifestation to malaria being an endemic region for malaria, that was in addition to many socio-economic factors. Similar to other studies, fever was constantly present.[16,17] Abdominal distension was presented in all of our patients which, was present in a lower percentage in other studies.[16,17] The gross splenomegally was the main reason for abdominal distension and all the expected signs were present in almost all of the patients. Lymphadenopathy was present in only one patient which, was similar to the low incidence described in Gizan,[17] but a much higher incidence of lymphadenopathy was described in Sudan.[19] In general, the clinical features were similar to that reported in Gizan, Saudi Arabia,[17] Sadah, Republic of Yemen,[16] Libya,[18] and Al-Baha, Saudi Arabia.[20]

Anemia was recorded in all patients which, was a known fact and similar to other studies,[16] however the high percentage of severe anemia (<5g/dl) could be explained by many other contributing factors mainly due to malaria and deficiency of hematinics. Neutropenia was more severe than described in a report from Gizan, most probably related to the delayed presentation which, either directly affected the bone marrow activity or due to the gross splenomegaly, though thrombocytopenia was less common. Half of the patients gave a history of receiving anti-malarial drugs, and around one 3rd had a positive malaria smear during the study period indicating the endemicity of malaria which further complicated the disease especially in delaying the diagnosis and consequently the appropriate therapy. Formol gel test was negative in the majority of our patients indicating that this non-specific test should not be relied on.[20] In most of the patients, the diagnosis was confirmed by the identification of leishmania donovan bodies in the splenic aspirate. This method was preferred if there was no contraindication as it was easy to perform, less painful and more importantly, the most sensitive.[2] There were no complications from both procedures.

After 20 days treatment with SS, the reasons for those patients who did not show up were most probably the improvement in the clinical manifestations and negative socio-economical factors. Half of those who came for follow-up after 20 days treatment were still positive for leishmania donovan bodies with clinical improvement. This was the reason for stopping the study at this stage as it was convincing to us that the 20 days of SS was not enough in this region for parasitological cure. Secondary bacteria infection was the cause of death of one patient, this gave a mortality rate of 5% (out of those with known follow-up) which was higher than that in other studies in Saudi Arabia[17,20] but lower than the mortality rate in some studies carried out in Sudan.[19,21] There were no complications observed from SS. There were no convincing explanations for the significant association between the positive formol gel test and abdominal distension, apart from the thought that this distension was due to huge splenomegaly which indicated a chronic course of the disease which in turn lead to an elevation of the globulin level. The significant association between cough and more blood transfusions in the malaria positive group was expected due to these 2 being manifestations of malaria.

In conclusion, 20 days treatment with SS was not adequate. Visceral leishmaniasis is a real health problem in children in Hajjah governorate. The clinical manifestations were similar to the Mediterranean type. The diagnosis may be delayed due to the endemicity of malaria and socio-economic factors. We would recommend that SS should not be given for less than 30 days until further studies are carried out confirming that the 30 day regimen is going to be adequate, in addition to follow up for detecting the relapse rate. Also, further health education for recognizing and consequently treating the disease as early as possible.

References

1. Al-Zahrani MA, Peters W, Evans DA, Smith V, Ching CI. Leishmania infecting man and wild animals in Saudi Arabia. Diversity of parasites causing visceral leishmaniases in man and dogs in the southwest. Trans R Soc Trop Med Hyg 1989; 83: 503-510.
2. WHO Expert Committee. The Leishmaniasis Geneva (Switzerland): WHO; 1984. Technical Report Series 701.
3. Hernandez PJ, Yebra BM, Jimenez ME, Sanz MC, Cuervas MV, Alonso PL et al. Visceral leishmaniases (Kala-azar) in solid organ transplantation: report of five cases and review. Clin Infect Dis 1999; 29: 918-921.
4. Delgado J, Macias J, Pineda JA, Corzo JE, Gonzalez-Moreno MP, de la Rosa R, et al. High frequency of serious side effects from meglumine antimoniate given without an upper limit dose for the treatment of visceral leishmaniases in human immunodeficiency virus type-1-infected patients. Am J Trop Med Hyg 1999; 61: 766-769.
5. Martino L, Robert ND, Raffella G, Silvestro S, Franscesco R, Elio Castagnola et al. Treatment of visceral leishmaniases in children with liposomal amphotericin B. J Pediatr 1997; 131: 271-277.
6. Giri OP, Singh AN. Experience with amphotericin-B in sodium stibogluconate-unresponsive cases of visceral leishmaniases in north Bihar. J Assoc Physicians India 1994; 42: 690-691.
7. Jha TK, Sundar S, Thakur CP, Peter B, Juntra K, Christina P et al. Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniases (see comments). N Eng J Med 1999; 341: 1795-1800.
8. Badaro R, Jones TC, Lorenco R, Cerf BJ, Sampaio D, Carvalho FM et al. A prospective study of visceral leishmaniases in an endemic area of Brazil. J Infec Dis 1986; 154: 639-649.
9. Maru M. Clinical and laboratory features and treatment of visceral leishmaniases in hospitalized patients in northwestern Ethiopia. Am J Trop Med Hyg 1979; 28: 15-18.
10. Thakur CP, Bhowmick S, Dolfi L, Olliaro P. Aminosidine plus sodium stibogluconate for the treatment of Indian kala-azar: a randomized dose-finding clinical trial. Trans R Soc Trop Med Hyg 1995; 89: 219-223.

11. Zijlstra EE, Siddig AM, El-Hassan AM, Hofland HW, El-Toum I, Satti M et al. The treatment of kala-azar in the Sudan with sodium stibogluconate: a randomized trial of three dosage regimens. Trans R Soc Trop Med Hyg 1993; 87: 307-309.
12. Benjamin B, Annobil SH, Bassuni WA. Diagnostic and management problems in childhood visceral leishmaniases in southwest Saudi Arabia. Ann Trop Paediatr 1994; 14: 7-13.
13. Nyakundi PM, Wasunna KM, Rashid JR, Gachih MJ, Kirigi G, Muttunga J. Is one year follow-up justified in kala-azar post-treatment. East Afr Med J 1994; 71: 453-459.
14. Thakur CP, Sinha GP, Sharma V, Pandey AK, Kumar M, Verma BB. Evaluation of amphotericin B as a first line drug in comparison to sodium stibogluconate in the treatment of fresh cases of kala-azar. Indian J Med Res 1993: 97: 170-175.
15. Seaman J, Pryce D, Sondorp HE, Moody A, Bryceson AD, Davidson RN. Epidemic visceral leishmaniases in Sudan: a randomized trial of aminosidine plus sodium stibogluconate versus stibogluconate alone. J Infect Dis 1993; 168: 715-720.
16. Elsheikh A, Mahgoub M, Al-Kebsi A. Visceral Leishmaniases in Children. The Medical Journal of Cairo University 1996; 64: 1007-1011.
17. Al-Orainy IO, Gasim IY, Singh LM, Badruddin I, Sylvester OU, Dhananjaya G et al. Visceral leishmaniases in Gizan, Saudi Arabia. Annals of Saudi Medicine 1994; 14: 396-398.
18. Mehabresh MI, El-Mauhoub MM. Visceral leishmaniases in Libya review of 21 cases. Ann Trop Paediatr 1992; 12: 159-163.
19. Zijlstra EE, Ali MS, El-Hassan AM, El-Toum IA, Satti M, Ghalib HW. Clinical aspects of kala-azar in children from the Sudan: a comparison with the disease in adults. J Trop Pediatr 1992; 38: 17-21.
20. Al-Juryan NA, Al-Ayed IH, Al-Nasser MN, Al-Mugeiren MM, Al-Mugeiren MM, Boohene AG, Al-Herbish AS. Visceral leishmaniases in infancy and childhood epidemiology and clinicopathological study of 63 cases in Al-Baha province, Saudi Arabia. J Trop Pediatr 1992; 38: 12-16.
21. Seaman J, Mercer AJ, Sondorp HE, Herwaldt BL. Epidemic visceral leishmaniases in southern Sudan: treatment of severely debilitated patients under wartime conditions and with limited resources. Ann Intern Med 1996; 124 : 664-672.