Visceral Leishmaniasis during Childhood in Southern Greece

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Records were reviewed of 82 immunocompetent children (median age, 2.5 years) from southern Greece who were diagnosed with visceral leishmaniasis from 1986 through 1998. Forty-nine (58%) patients originated from the city of Athens; of them, 46 (94%) lived by hills bordering the city. The median interval from the onset of symptoms to admission was 10 days. Fever and splenomegaly were observed in >95% of the patients. Thrombocytopenia was the most frequent hematological finding (80%). All patients were treated with meglumine antimonate; 20 (24%) of them were partially treated on an outpatient basis. Rapid clinical response was noted in all patients but one. Five patients relapsed; 3 responded to reintroduction of meglumine antimonate, 1 responded to liposomal amphotericin B, and 1 underwent splenic artery ligation. We conclude that pentavalent antimonials remain the first choice of treatment for visceral leishmaniasis in immunocompetent children in areas where resistance has not become a problem. It is possible to treat affected patients with outpatient administration of these agents, making them feasible options for therapy.

Visceral leishmaniasis is endemic in areas bordering the Mediterranean Sea. The intracellular protozoan Leishmania infantum is the causative agent, and transmission is via dogs through hematophagous sandflies. Infection is spread throughout the reticuloendothelial system and typically presents as fever, hepatosplenomegaly, pancytopenia, and progressive deterioration of the host [1, 2].

For many decades, pentavalent antimonials constituted the standard treatment for visceral leishmaniasis. These agents have been used extensively in children and have been demonstrated to be efficacious and safe. During the last decade, however, the emergence of strains of microorganisms resistant to pentavalent antimonials has prompted the evaluation of alternative therapeutic agents, including pentamidine, interferon gamma, and liposomal amphotericin B [2–5].

Visceral leishmaniasis must be reported in Greece. However, detailed information on children remains unknown. During the 1985–1994 period, the annual incidence rate in the general population was 1.12 cases per 100,000 residents, and 1.23 cases per 100,000 children in the area of Athens. The relative annual incidence for children aged ≤14 years was 3.2 cases per 100,000 children. We retrospectively reviewed our experience with visceral leishmaniasis in children, with special emphasis on epidemiological features and response to treatment.

Patients and Methods

P. & A. Kyriakou Children’s Hospital is a 510-bed university tertiary-care hospital in Athens. It provides medical services to ~800,000 pediatric residents in Athens in association with the only other 800-bed pediatric hospital in this area. In addition, the hospital serves as a referral pediatric hospital for the greater region of southern Greece. All children aged 0–14 years with visceral leishmaniasis diagnosed from January 1986 through December 1998 were identified through a computerized database system. Only immunocompetent patients were included in the study.

Visceral leishmaniasis was defined as identification of the amastigote form of leishmania in bone marrow smear, positive serological test (immuno-fluorescence antibody test), or both in a patient with manifestations compatible with visceral leishmaniasis (i.e., fever, hepatosplenomegaly, anemia, leukopenia, and thrombocytopenia). Fever was defined as a temperature ≥38.0°C. Anemia was defined as a hemoglobin value of <9.0 mg/dL. Leukopenia was defined as <4000 WBCs/mL of blood, and thrombocytopenia as <150,000 platelets/mL. Patients were considered to have achieved hematological restoration if we noted recovery of their WBC count (≥4000 neutrophils/mL), platelet count (≥150,000 cells/mL), and hemoglobin (≥9.0 mg/dL). Clinical response was assessed at the completion of treatment and was defined as cure (defervescence, restoration of laboratory parameters, or significant reduction of spleen size) or failure (persistent or worsening clinical and laboratory findings). Relapse was defined as the reappearance of signs and symptoms of infection in association with identification of amastigote forms of leishmania in bone marrow smear after initial successful treatment.

Meglumine antimonate (glucantime) was administered intramuscularly at a dosage of 20 mg/kg of pentavalent antimony per day after a gradually increasing daily dose during the first 4 days.

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of therapy, for a total of 21 or 30 days (the latter given daily for 15 days, followed by no treatment for 15 days, then daily for 15 days). The decision to choose the 21-day or the 30-day course was based on the physician’s preference. Liposomal amphotericin B was administered at 2 mg/kg/day for 28 days (1 patient during 1993) or at a total dose of 14 mg/kg (1 patient during 1997).

During the first 5 years of the period under study, electrocardiograms were occasionally performed for patients who received meglumine antimonate. Beginning in 1991, electrocardiograms were routinely performed for all patients 7–10 days after treatment was introduced and whenever indicated by clinical findings. All patients were followed at the outpatient clinic of the hospital for at least 1 year after treatment was completed. While preparing this article, whenever feasible, we contacted patients via telephone to gather further follow-up data.

Results

During the period under study, 82 children (51 boys) were diagnosed with visceral leishmaniasis. Admissions were evenly distributed through the years studied. The patients’ median age was 2.5 years (range, 5 months–13 years); 8 patients (10%) were distributed through the years studied. The patients’ median age diagnosed with visceral leishmaniasis. Admissions were evenly distributed through the years studied. The patients’ median age was 2.5 years (range, 5 months–13 years); 8 patients (10%) were aged <12 months. Twelve patients (15%) were immigrants (8 from Albania, 2 from Russia, 1 from Africa, and 1 from the Philippines).

Forty-nine (58%) of the patients were from Athens, and 33 (42%) were from areas evenly distributed in 25 rural or suburban areas in southern Greece. Of the patients living in Athens, 46 (94%) lived in districts that were located by the foothills of mountains bordering the city and the hills within the city itself (figure 1). Because stray dogs and sandflies coexisted in these areas, we believe that these patients contracted leishmaniasis at their area of residence. Two additional patients from Athens were presumably infected during domestic holidays, and the source of infection remained unknown in another patient. In total, all 72 patients for whom information was available contracted the disease in Greece. For 1 patient, the development of visceral leishmaniasis was preceded by the disease in 1 parent. No other intrafamily cluster was observed.

Evaluation of access to medical services by the patients we studied revealed that 22% of them had received none of the vaccinations recommended for their age group, and 15% had no medical insurance. Analysis of the nutritional status of the patients showed that 16% were below the tenth percentile on the height-for-age growth charts, and 10% of them below the fifth percentile. On to weight-for-age growth charts, 22.5% of the patients were below the tenth percentile and 14.5% below the fifth percentile.

A tendency toward the onset of symptoms during spring or summer was observed (67% of cases). The median time from the onset of symptoms to admission was 10 days (range, 1 day–8 months); 80% of the patients experienced symptoms for <1 month. Fever and splenomegaly were observed in >95% of the patients (table 1). The most frequently encountered hematological finding was thrombocytopenia (80%), followed by anemia (77%). Thirty-four (41.5%) of the patients had a concurrent bacterial or viral infection, including acute otitis media (10 patients), upper respiratory infection (10 patients), pneumonia (5 patients), urinary tract infection (3 patients), and tonsillitis, gastroenteritis, herpes simplex virus stomatitis, respiratory syncytial virus bronchiolitis, active hepatitis B, and measles (1 patient each). Appropriate antimicrobial treatment was administered to 19 of these patients. In addition, antibacterial agents had been administered to 17 (21%) patients before admission.

Diagnosis of visceral leishmaniasis was established by bone marrow direct microscopy in association with positive serology in 80 patients and serologically only in 2, at a median of 1 day (range, 0–13 days) after admission. All 82 patients were treated with meglumine antimonate; 47 patients received treatment for 21 days and 35 patients received treatment for 30 days. Because of persistent fever, interferon gamma was added to 1 patient’s treatment course, and defervescence followed. Twelve (15%) patients underwent blood transfusion. Taking into consideration the clinical situation of the patients in association with socioeconomic parameters indicative of compliance, 20 (24%) patients were partially treated on an outpatient basis.

All patients were cured with meglumine antimonate except 1, whose spleen remained enlarged. The remaining 81 (99%) patients noted reduction of spleen size—up to half of the initially palpated size—within a median of 13 days (range, 6–30 days) after treatment was begun. Overall, all 82 patients became afebrile a median of 3 days (range, 1–13 days) after treatment was initiated, whereas hematological restoration occurred a median of 12 days later (range, 5–30 days).

Patients were followed at the outpatient clinic for a median of 1 year (range, 1–6 years) after treatment was completed. In addition, we contacted 34 patients by telephone as we prepared this article. Five (6%) patients had a relapse of visceral leishmaniasis within the next 3–12 months. These included 4 (8.5%) of 47 patients initially treated with 1 21-day course of meglumine antimonate and 1 (3%) of 35 patients who received 2 15-day courses of treatment. Reintroduction of meglumine antimonate resulted in successful treatment in 3 patients (60%). Of the remaining 2 patients, one later responded to liposomal amphotericin B; however, the other, who had persistent splenomegaly, did not, and this patient later underwent splenic artery ligation. No other treatment was administered to this patient.

No relapse of leishmaniasis or splenic artery ligation–related complications occurred in this patient in the 6 years of follow-up. Furthermore, of 5 patients with relapse, 2 had a concurrent infection at the time of initial diagnosis, and 1 was completely unvaccinated and below the 10th and 5th percentiles according to height-for-age and weight-for-age growth charts, respectively. No other distinguishing characteristics were observed among them.

Adverse effects while receiving meglumine antimonate were observed in 15 (18%) patients, including rash (5 patients), dry
Figure 1. Geographical distribution of children with visceral leishmaniasis in the area of Athens, Greece. Each case of leishmaniasis is represented as a dot and is placed in the area of the patient’s residence.

All children acquired the disease in Greece. The fact that almost all children were infected at their areas of residence—rather than infected during domestic holidays—underlies the prolonged and strenuous contact with the vector required for the transmission and development of clinically apparent leishmaniasis to occur. In an epidemiological study of leishmaniasis in northeast Brazil, the exposure to an increased parasite burden was associated with progression to clinical disease [6]. In two-thirds of the patients we studied, we discovered that the onset of symptoms occurred during spring and summer, when children spend more time outdoors exposed to sandflies. Because a median duration of <2 weeks intervened from the onset of symptoms to full-blown leishmaniasis, we believe that the incubation period was short. Progression to full-blown leishmaniasis typically occurs within 3–8 months after infection [2].

However, similar proximal development with the patients we studied has been observed elsewhere [6].

The hills surrounding Athens and the city itself provide a

cough (4), induration at the injection site (4), diarrhea (2), and tachycardia (1). Of the 4 patients with cough, 3 had normal chest radiographs and 1 had interstitial markings. All adverse effects were transient and self-limited. No treatment discontinuation was required. No adverse effects were detected in the 2 patients treated with liposomal amphotericin B.

Discussion

To our knowledge, this is the first report of pediatric visceral leishmaniasis in Greece. The number of patients included in this report provides a reliable indication of leishmaniasis in Greece in general. We did not attempt to estimate the incidence of the disease. Because diagnosis and treatment are almost exclusively established in the hospital setting and a mean of 6 cases of leishmaniasis were admitted at our hospital per year, it would seem that leishmaniasis is rarely seen in children in southern Greece.
Table 1. Findings in 82 children with visceral leishmaniasis in southern Greece.

<table>
<thead>
<tr>
<th>Findings</th>
<th>No (%) of patients</th>
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<tbody>
<tr>
<td><strong>Clinical findings</strong></td>
<td></td>
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<tr>
<td>Splenomegaly</td>
<td>81 (99)</td>
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<tr>
<td>Fever</td>
<td>78 (95)</td>
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<tr>
<td>Hepatomegaly</td>
<td>70 (85)</td>
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<tr>
<td>Paleness</td>
<td>63 (77)</td>
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<tr>
<td>Anorexia</td>
<td>33 (40)</td>
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<tr>
<td>Lymph node enlargement</td>
<td>32 (39)</td>
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<tr>
<td>Weight loss</td>
<td>15 (18)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>15 (18)</td>
</tr>
<tr>
<td>Cough</td>
<td>13 (16)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Weakness</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (6)</td>
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<tr>
<td>Ecchymoses/gingival bleeding</td>
<td>2 (2)</td>
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<tr>
<td><strong>Laboratory findings</strong></td>
<td></td>
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<tr>
<td>Thrombocytopenia</td>
<td>66 (80)</td>
</tr>
<tr>
<td>Anemia</td>
<td>63 (77)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>51 (62)</td>
</tr>
<tr>
<td>Hyperglobulinemia</td>
<td>27 (100)a</td>
</tr>
<tr>
<td>Increased hepatic transaminases</td>
<td>19 (26)b</td>
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</tbody>
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*a Hyperglobulinemia occurred in 27 of 27 patients who had the test performed.
* Increased hepatic transaminases occurred in 19 of 72 patients who had the test performed.

favorable environment for maintaining and transmitting visceral leishmaniasis. A survey by the Greek Ministry of Health of 1005 cases of leishmaniasis from 1962 through 1992 in the area of Athens found that ~90% of the cases concerned patients living near the quarries on these hills [7]. In Athens, transmission is likely sustained by an ecological niche of scrub areas with rock formations that contain cracks, holes, and caves that serve as lodges for stray dogs and sandflies; here, infected dogs act as reservoir for infection of sandflies (figure 2). Children are infected while playing in this environment during spring and summer.

The role of the intrinsic factors of the host in the development of visceral leishmaniasis appears crucial. Young age, male sex, and deficient nutrition have been implicated in the promotion of clinically apparent disease after infection [2, 6]. The majority of children in this study were aged <3 years and boys. In addition, a nonnegligible number of the patients we studied were malnourished. The precise mechanism of the association between malnutrition and development of symptomatic visceral leishmaniasis has not yet been clarified; however, both a leishmania-induced effect and a more chronic course reflecting economic deprivation of the host appears to exist [8]. Control of asymptomatic infection is mainly accomplished through T cell–mediated immune responses, and malnutrition has a negative impact on this component of immunity [9–11]. The fact that >40% of the patients we assessed had a concurrent infection at the time of admission underlies their susceptibility to infectious diseases. Finally, approximately one-fourth of the patients had restricted access to medical services and were of very low economic status, as indicated by their deficient vaccination status and the absence of medical insurance.

Meglumine antimonate was highly effective as the first-choice treatment of visceral leishmaniasis in these pediatric patients. Ninety-nine percent of them were cured. Clinical response was rapid. However, the optimal treatment duration with pentavalent antimonials has not been established. The World Health Organization recommends 20–30 days of administration [1]. In the present study, 6% of the patients treated with meglumine antimonate suffered a relapse. It is of note that almost all of these were patients treated with a single 21-day course instead of a 30-day course. The fact that a second course of meglumine antimonate resulted in the cure of an additional 60% of the patients in instances of relapse indicates that the initially observed therapeutic failure might actually be attributed to incomplete parasitologic clearance as a result of undertreatment, rather than resistance to the regimen itself. The proportionally large size of reticuloendothelial system compared to body size in children with visceral leishmaniasis may explain the higher doses of pentavalent antimonials required for their cure. Differences in cure rates in relation to treatment duration have also been observed in several endemic areas and are mainly attributed to the clinical situation of the patients at the time of diagnosis, but the different leishmania species may also affect the cure rate [1, 2, 12]. It is suggested, therefore, that adoption of a specific regimen should be based on previous experience within a specific region, a specific group of patients, and a specific leishmania species [11]. Finally, the use of meglumine antimonate in these pediatric patients appeared to be safe.

Another alternative for the treatment of visceral leishmaniasis is liposomal amphotericin B. Two recent studies showed that liposomal amphotericin B at a total dose of 18 mg/kg (3 mg/kg/day on days 1–5, and 10) was effective and safe in children with visceral leishmaniasis caused by L. infantum [4, 13]. The US Food and Drug administration recently approved li-
posomal amphotericin B for the treatment of immunocompetent patients with visceral leishmaniasis at a total dose of 21 mg/kg (3 mg/kg/day on days 1, 2, 3, 4, 5, 14, and 21) [14]. The short treatment duration of 5–10 days renders posomal amphotericin B a more attractive therapeutic regimen, especially for children, in contrast to the inconvenient and prolonged treatment with pentavalent antimonials. In our hospital, to avoid inconveniencing patients, we adopted an outpatient treatment policy for selected patients that used pentavalent antimonials in which parents were responsible for visiting the outpatient clinic every day, with satisfying results.

The main obstacle to the use of posomal amphotericin B is its significantly high cost. Indeed, the average cost of treating a 2.5-year-old child with a mean weight of 13 kg in our hospital is about $810 for posomal amphotericin B, compared with about $7 for meglumine antimonate. In practice, the cost of treating 1 child with posomal amphotericin B is equivalent to the cost of treating an additional 114 children with pentavalent antimonials. In developing countries, the wide use of posomal amphotericin B to treat children with visceral leishmaniasis appears to be prohibitively expensive. Unfortunately, the emergence of visceral leishmaniasis that is resistant to pentavalent antimonials has been documented in this part of the world [11, 12]. Therefore, selecting the appropriate treatment regimen on the basis of cost-effectiveness studies appears imperative. Furthermore, the oral route of treatment may be of great importance. A recent phase I/II trial in adult patients in India showed that the oral agent miltefosine administered at a dosage of 100–150 mg/day for 28 days was ~100% effective and acceptably safe [15].

Considering the efficacy and safety of pentavalent antimonials in the pediatric patients we studied, we suggest that these agents remain the first-choice treatment for visceral leishmaniasis in immunocompetent children in areas where resistance has not become a problem. After initial clinical and hematological improvement, patients can be treated on an outpatient basis. Electrocardiograms should be routinely performed between day 7 and day 10 of treatment with meglumine antimonate and as indicated by clinical findings. We also suggest that prospective randomized trials be conducted to define and compare the efficacy, toxicity, and cost of pentavalent antimonials to posomal amphotericin B for the treatment of visceral leishmaniasis in children.

References