Pediatric visceral leishmaniasis in Albania

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Objective: Visceral leishmaniasis (VL) in children is endemic in southern Europe but has not been previously reported from Albania. This prospective study reports the clinical and laboratory findings in 50 children with visceral leishmaniasis, the value of a direct agglutination test (DAT), and the result of treatment with meglumine antimonate.

Materials and Methods: Sera obtained from 50 children with VL confirmed by bone marrow examination, 40 household contacts, and 30 hospitalized children with other infections were examined using DAT.

Results: Clinical features included fever (100%), hepatosplenomegaly (100%), pallor (100%), weight loss (98%), vomiting (68%), diarrhea (32%), and bleeding disorders (8%). Laboratory findings were anemia (94%), neutropenia (85%), hypergammaglobulinemia (70%), and thrombocytopenia (22%). Thirty children who developed secondary bacterial infections had significantly lower hemoglobin and neutrophil counts (P<0.0001). Direct agglutination test had a sensitivity of 98%, a specificity of 100%, and a positive predictive value of 100%. One child with severe generalized bleeding died within 48 hours of admission before receiving treatment.

Conclusion: The direct agglutination test was highly valuable in diagnosis of VL in this series. Meglumine antimonate was an effective therapeutic agent. Post-treatment bone marrow examination confirmed recovery in all patients. There were no relapses of VL during one-year follow up.

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Visceral leishmaniasis (VL) in children is reported from many regions of the world.1-10 Although it is endemic in Albania, it has not been previously reported. Therefore, a prospective study was designed at the University Hospital Center of Tirana to describe the clinical features of VL in children and to evaluate the diagnostic accuracy of the direct agglutination test (DAT) and the results of treatment with meglumine antimonate (Glucantime, Rhône Poulenc, Paris).

PATIENTS AND METHODS

The study group consisted of 50 children with visceral leishmaniasis confirmed by the presence of amastigotes in Giemsa-stained bone marrow aspirate. Forty healthy household contacts and 30 pediatric patients served as controls. Parental consent was obtained for each child. The sera obtained from the patients with VL and the control groups were examined by DAT. A leishmania antibody titer greater than 1:3200 was considered positive.

All patients with VL were treated with daily intramuscular injections of meglumine antimonate (60-80 mg/kg/24 h, equivalent to 20 mg Sb5+/kg/24 h) for 21 consecutive days. A bone marrow examination was done at the end of treatment. Patients with a positive bone marrow examination after the first cycle of treatment received meglumine antimonate for an additional 10 days after a 2-week interval. Children with severe anemia or pancytopenia were given blood transfusions. Children with secondary bacterial infections received antibiotic therapy. Patients were reexamined at 1, 6, and 12 months following discharge.

RESULTS

Thirty boys and 20 girls with VL, ranging in age from 4 months to 12 years (mean, 2.55 y) were admitted to the Section of Pediatric Infectious Diseases at the University Hospital Center of Tirana. Two infants (4%) were 4 to 6 months, 13 (26%) were 7 to 12 months, 11 (22%) were 13 to 18 months, 10 children (20%) were 2 to 5 years, and 3 (6%) were more than 5 years old.

Patients were referred from all parts of the country, especially from the north, where the infection is more prevalent. Duration of symptoms before admission ranged from 2 weeks to 8 weeks. Children presented with pallor (100%), hepatosplenomegaly (100%), and hyperthermia (100%). Thirty-five (70%) had a fever of more than 39°C associated with perspiration and chills. There was considerable splenomegaly, ranging from 4 to 12 cm. Twenty-four children (48%) had a palpable
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spleen larger than 7 cm. Weight loss was observed in 49 patients (98%), vomiting in 34 (68%), diarrhea in 16 (32%), and bleeding disorders and lymphadenopathy in 4 (8%) patients.

Laboratory examination revealed 47 (94%) children with a hemoglobin level of less than 10 g/dL, 24 (48%) with a hemoglobin level of less than 7 g/dL, 45 (90%) with erythrocyte sedimentation rate higher than 30 mm/h, 44 (85%) with neutropenia (<1500/mm³), 37 (74%) with leukopenia (<4000/mm³), 35 (70%) with gammaglobulinemia (>2 g/dL), 11 (22%) with a platelet count less than 100,000/mm³, and 11 (22%) with serum transaminase levels higher than 50 IU/L.

Thirty children (60%) developed associated bacterial infections: 20 with pneumonia, four with pneumonia and enteritis, three with pneumonia and otitis, one with gastroenteritis, one with otitis media, and one with soft-tissue abscess. The most commonly isolated microorganisms were Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa, Salmonella enteritidis, and Salmonella typhimurium. There was no significant difference in the mean age of children with or without secondary bacterial infections; however, children who developed complications had significantly lower levels of hemoglobin and neutrophils (Table 1).

A 15-month-old boy with generalized bleeding presented with a 5-fold increase in alanine and aspartate aminotransferase values, prolonged prothrombin time (40 s), serum protein of 4 g/dL, and hypoproteinemic edema. Serologic studies for viral hepatitis A, B, and C were negative. The patient died 2 days after admission before receiving treatment.

Direct agglutination test examinations revealed an antibody titer higher than 1:3200 in 49 (98%) patients. Forty (80%) patients had a DAT-titer higher than 1:100,000. In all individuals in the control group, DAT was nonreactive (<1:800). A 4-month-old baby was the only patient with a nonreactive serology. In this study, it had a sensitivity of 98%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 98%.

Meglimine antimonate (Glucantime; Rhône Poulenc, Paris) was well tolerated with no adverse effects. Forty (80%) patients responded to 21 days of treatment, whereas the remaining nine (18%) patients required an additional 10 day-course of treatment after a two-week interval. Clinical response, confirmed by the remission of fever, appeared approximately 5 to 8 days after the onset of treatment. Improvement in hematologic parameters appeared in the second and third week of treatment. Bone marrow studies at the end of treatment confirmed recovery in all children. None of the patients had a relapse during the one-year follow-up period.

**DISCUSSION**

Leishmaniasis denotes a group of varied syndromes caused by a number of species of the protozoa Leishmania. There is an overall prevalence of 12 million cases of leishmaniasis worldwide. The global incidence of visceral leishmaniasis is 500,000 new cases per year. Children acquire VL either by living in endemic areas or by travelling to those regions. In Albania, children comprise 70% of patients with VL. The incidence of VL in the patients in the present study was highest in the first 2 years of life, similar to that reported from North Africa and Pakistan. Other southern European countries, however, have reported a wider age range.

Patients with human immunodeficiency virus or acquired immunodeficiency syndrome (HIV/AIDS) are at greater risk of acquiring leishmaniasis. A study from Alps Maritime in France, reported that 40% of adults with VL were HIV seropositive and that children represented only 28% of all patients. Although HIV serology was not done in these children, the higher incidence of VL in infants and children appears to be attributable to the prevalence of malnutrition and a smaller number of adults with HIV/AIDS in Albania.

Anemia is common in children with VL. Consumption of iron bound to lactoferrin, transferrin, or hemin by the promastigotes may be one of the contributing factors.

Secondary bacterial infections were found in 30 (60%) patients. Respiratory and gastrointestinal tract infections were the most common. These infections are associated with the depression of cell-mediated immunity to leishmanial antigen and the presence of serum suppressor factors capable of suppressing the immune response. In the present study, patients with bacterial infections manifested significantly lower white blood cell count (WBC) and neutrophils (P<0.0001). In addition, these children were often malnourished, and they presented with anemia. The only child with fatal outcome in this study presented with hepatic complication and generalized bleeding.

The direct agglutination test is highly valuable. In the present study, it had a sensitivity of 98%, specificity of 100%, and positive predictive value of 100%, whereas positive bone marrow aspirate confirms the diagnosis of VL in 72 to 93% of patients. The absence of antibody response in the 4-month-old infant could have been attributable to his young age. The culture of

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**Table 1. Mean age and hematological parameters in patients with and without secondary bacterial infections**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>With bacterial infections</th>
<th>Without bacterial infections</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (mo)</td>
<td>25</td>
<td>34</td>
<td>&gt;0.21</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>6.76</td>
<td>8.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WBC/mm³</td>
<td>4300</td>
<td>6500</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neutrophils/mm³</td>
<td>1300</td>
<td>2058</td>
<td>&lt;0.0001</td>
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bone marrow aspirate from patients with leishmaniasis in Albania isolated taxonomic complex of Leishmania infantum, zymodeme MON = 1. The children were examined at 1, 6, and 12 months following discharge. There were no relapses.

CONCLUSIONS

Visceral leishmaniasis (L. infantum, zymodeme MON = 1) is endemic in Albania and is found predominantly in infants and children. Fever, hepatosplenomegaly, pallor, and anemia are common findings. Lower hemoglobin and WBC values were associated with the acquisition of bacterial infections. In this study, DAT had a sensitivity of 98%, specificity of 100%, and positive predictive value of 100%. All children were treated with meglumine antimonate and responded well. They were followed for one year with no relapses of VL.

REFERENCES