Childhood visceral leishmaniasis complicated by bacterial infections

M.R. Kadivar,[1] T.Z. Kajbaf,[1] A. Karimi [1] and A. Alborzi [1]

داء الليشمانيات الحشوي المتفاقم بعدوى جرثومية في الأطفال

محمد رحيم كاديفار وطاهرة ضيائي كاجباف وعبد الله كريمي وعبد الوهاب البرزي

خلاصة: العدوى الجرثومية المضافة هي إحدى المضاعفات الرئيسية التي تؤدي إلى وفاة المصابين بداء الليشمانيات الحشوي. ولقد درسنا تواتر العدوى الجرثومية وأنواعها في 54 مريضاً أدخلوا المستشفى بداء الليشمانيات الحشوي. وكان المرضى أطفالاً تتراوح أعمارهم بين ثلاثة أشهر ونصف الشهر وبين سبع سنوات. ووجدت أنواع من العدوى الجرثومية في 22 مريضاً (41%). وقد تم استفراد (عزل) الجراثيم من المصابين بالالتهاب الرئوي والإنتان الدموي والتهاب الأذن الوسطى وعدوى المسالك البولية والعدوى الجلدية. وكانت الجراثيم التي عزلت أكثر من غيرها هي الأمعائيات. وتبيّن أنه في الرضّع المصابين بداء الليشمانيات الحشوي، يمكن أن تكون حالات العدوى الجرثومية القاتلة مصحوبة بعلامات وأعراض غير نوعية. وهكذا فمن الأهمية بمكان أن تبدا المعالجة بالمضادات الحيوية في وقت مبكر.

ABSTRACT Bacterial superinfection is one of the major complications leading to death in patients with visceral leishmaniasis. We studied the frequency and type of bacterial infection in 54 patients admitted to hospital with visceral leishmaniasis. The patients were children who ranged in age from 3½ months to 7 years. Bacterial infections were found in 22 (41%) of the patients. Bacteria were isolated in patients with pneumonia, septicaemia, otitis media, urinary tract infections and skin infections. *Enterobacteriaceae* were the most common bacterial agents isolated. In infants with visceral leishmaniasis, fatal bacterial infections can be accompanied by nonspecific signs and symptoms. Thus, it is important to initiate antibiotic treatment early.

La leishmaniose viscérale infantile compliquée par des infections bactériennes

RESUME La surinfection bactérienne est l'une des complications majeures entraînant la mort chez les patients atteints de leishmaniose viscérale. Nous avons étudié la fréquence et le type des infections bactériennes chez 54 patients hospitalisés avec une leishmaniose viscérale. Les patients étaient des enfants dont l'âge était compris entre 3 mois et demi à 7 ans. Des infections bactériennes ont été trouvées chez 22 patients (41%). Des bactéries ont été isolées chez des patients atteints de pneumonie, de septicémie, d'otite moyenne, d'infections urinaires et d'infections cutanées. Les *Enterobacteriaceae* étaient les agents bactériens les plus couramment isolés. Chez les nourrissons atteints de leishmaniose viscérale, les infections bactériennes mortelles peuvent s'accompagner de signes et symptômes non spécifiques. Il est donc important de mettre en route le traitement antibiotique rapidement.

[1]*Department of Paediatric Infectious Diseases, Shiraz University of Medical Sciences, Shiraz, Islamic Republic of Iran.*

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Introduction

Visceral leishmaniasis (kala azar) is a severe protozoan disease that is found in the tropics and subtropics. It is endemic in southern Islamic Republic of Iran where most of the patients are referred to the Shiraz Paediatric Hospital. The disease is characterized by: fever, weight loss, lassitude, pallor, hepatosplenomegaly, anaemia, leukopenia and hypergamma-globulinaemia [*1*].

Immunological disorders such as depression of cell-mediated immunity are predisposing factors for visceral leishmaniasis [*2*]. Untreated visceral leishmaniasis is fatal in about 80% of children. The most common complications are bacterial infections and bleeding. Bacterial infections have been reported in up to 52% of patients with visceral leishmaniasis, and are the most common causes of death in advanced cases [*3*]. Knowledge of the frequency and types of infections will help us better manage patients with visceral leishmaniasis.

Patients and methods

We studied 56 children with visceral leishmaniasis admitted to the Paediatric Hospital of Shiraz University of Medical Sciences from December 1996 to February 1998. Of the 56 patients, 2 were also diagnosed with leukaemia. Since leukaemia is an important factor for bacterial infections, they were excluded from the study. There were 30 males and 24 females in the study ranging in age from 3½ months to 7 years with a mean age ± standard deviation of 16 ± 13.9 months.

Visceral leishmaniasis was suspected in every patient who came from an endemic area who presented with prolonged fever, pallor and hepatosplenomegaly. Visceral leishmaniasis was also confirmed by an indirect immunofluorescent antibody test which gave a titre of ≥ 1/128 and/or a positive bone marrow aspiration [*4*].

All the patients were examined for signs of infection on the first day of admission. At that time, the following procedures were requested for all patients: a complete blood count, determination of sedimentation rate and C-reactive protein, febrile agglutination test, liver function tests, culture of blood, urine and stool, and a chest X-ray. Stool specimens were cultured in order to isolate pathogenic bacteria such as *Salmonella*, *Shigella* and pathogenic *Escherichia coli*.

Due to the difficulty in carrying out invasive procedures such as lung puncture and tympanocenthesis in infants and children, respiratory tract infections were diagnosed by clinical manifestations and chest X-ray in cases of pneumonia. In the patients with complicated pneumonia, perforated necrotic otitis media and pyoderma, pleural effusion, ear discharge and skin lesions were cultured.

Abdominal sonography was performed on 46 patients. An antibiotic sensitivity test was performed for each isolate; however, the number of isolates was not statistically sufficient to report sensitivity results.

Results

The mean duration of illness was 57 ± 45.0 days before admission. Bacterial infections were found in 22 (41%) of the 54 patients with visceral leishmaniasis, the sites of which are listed in Table 1. Pneumonia, septicaemia, otitis media, urinary tract infections and skin infections were the common infections found in the patients. A variety of infective agents were isolated from different sites. Bacteria were isolated in 14 patients (26%), mostly of the family *Enterobacteriaceae* (50%) (Table 2). There

Table 1 **Sites of bacterial infection in 22 of the 54 patients with visceral leishmaniasis**

Site	No.	%
Lower respiratory tract	10	18.5
Blood	7	13.0
Middle ear	5	9.3
Urinary tract	4	7.4
Skin	1	1.9

Table 2 **Types of infection and bacteria isolated in patients with visceral leishmaniasis**

Type of infection	No.	Bacteria	No.
Septicaemia	7	*Staphylococcus aureas*	3
		Klebsiella pneumoniae	2
		Pseudomonas aeruginosa	1
		Enterobacter	1
Urinary tract infection	4	*Escherichia coli*	
		Enterobacter	1
Empyema	1	*S. aureus*	1
Otitis media	1	*P. aeruginosa*	1
Cutaneous infection	1	*P. aeruginosa*	1

Table 3 **Frequency of bacterial infection in patients with visceral leishmaniasis according to neutrophil count**

Neutrophil count	Bacterial infection No.	%
< 500/mm^3	6/9	67
≥ 500/mm^3	16/45	35

Fisher exact test P-value = 0.136.

were 15 patients with pyuria (white blood cell count > 5 per high-powered field); *E. coli* was isolated in 3 of them and enterobacter in one.

Granulocyte counts of ≤ 500/mm^3 were observed in 9 patients (17%) with visceral leishmaniasis and 6 of those (67%) had a bacterial infection. Granulocyte counts of ≥ 500/mm^3 were seen in 45 patients (83%) with visceral leishmaniasis, and 16 of the patients (35%) in this group also had a bacterial infection. There was no significant correlation between bacterial infection and granulocyte count (P = 0.136) (Table 3). More than half (55%) of the patients were below the fifth percentile in the normal growth chart, but none of them had clinical evidence of kwashiorkor or marasmus. Abdominal sonography showed no evidence of intra-abdominal infection. All the patients were anaemic, had a reversed albumin/globulin ratio, positive C-reactive protein and an erythrocyte sedimentation rate > 30 mm/hour.

Discussion

There are many reasons for a high incidence of bacterial infections in patients with visceral leishmaniasis. Malnutrition and leukopenia are two reasons for the disease. There are many immunological factors including: 1) depression of cell-mediated immunity due to leishmania antigens and other non-related antigens [*2,5–8*]; 2) presence of serum suppression factors; and 3) nonspecific polyconal B-cell activation with autoantibody production due to predominant Th_2 cell activation in comparison with Th_1 cell activation and the presence of high levels of immune complexes [*9,10*].

The incidence of bacterial infection in our patients with visceral leishmaniasis was 41%. This is lower than the 52% reported

by Guerreiro [3] and 60% reported by Andrade [11]. The lower frequency in our study may be due to: 1) we considered bacterial infection only on the first day of admission; 2) the use of antibiotics before admission; and 3) the lower number of neutropenic patients in our study.

Respiratory tract infection and septicaemia were the most common types of infection, 18.5% and 13.0% respectively. If we consider previous antibiotic therapy as an important cause of sterile pyuria, the most common bacterial infection was urinary tract infection. The Guerreiro study found that the lower respiratory tract was the most common site of bacterial infection followed by the urinary tract [5]. The Andrade study found that the skin and the lower respiratory tract were the most common sites [11]. In these studies, a urine culture was not carried out in patients who had no pyuria in urinalysis.

Both Gram-positive and Gram-negative bacteria were isolated from various samples, mostly *Enterobacteriaceae*. Due to the small number of neutropenic patients in our study, no significant difference was found between the patients and those with granulocytes > 500/mm^3. However, because of the higher mortality of febrile neutropenic patients with bacterial infection, and due to the severity and nonspecific signs and symptoms of bacterial infections in infants, appropriate empirical therapy should be started after collecting necessary specimens. The antibiotics given should be effective against both Gram-positive and Gram-negative microorganisms.

Based on antibiotic sensitivity results and clinical experiences, a combination of ampicillin and gentamicin are the most commonly used antibiotics in all infants with visceral leishmaniasis for the coverage of common microorganisms. It should be emphasized that in very ill and/or neutropenic patients (< 500/mm^3) and in patients with *Staphylococcus aureus* or *Pseudomonas aeruginosa* infection, antibiotics such as ceftazidime and vancomycin should be given.

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