Update Article

MANAGEMENT OF KALA AZAR - AN UPDATE

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ABSTRACT

Kala azar continues to be a medical problem in India and with the increase in incidence of HIV Infection it is likely that kala azar will be encountered more frequently and in its atypical forms. To aid diagnosis, several immunological tests are now available and they are more sensitive and specific than the aldehyde test. Like many other diseases today, the treatment of kala azar is hampered by drug resistance. Newer drugs are available and so are new delivery systems. Kala azar develops frequently in the HIV infected person before development of AIDS. The presentation is atypical and leishmanial species other than *L. donovani* may also be the infecting agents. A combination of sandfly control, detection and treatment of patients and prevention of drug resistance continues to the ideal approach for the control of the disease.

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WHO estimates that more than 200 million people in the world are exposed to leishmanial parasites and more than 500,000 people develop clinical visceral leishmaniasis each year [1]. Major epidemics have occurred in the eastern part of our country and some other parts of the world [2]. Large scale drug failure has been the outstanding feature of the Indian epidemic of 1991, leading to increased morbidity and mortality. Certain clinical manifestations like lymphadenopathy which were not seen in Indian kala azar earlier, have been reported from Bihar and West Bengal [3]. With the increasing incidence of HIV infection, more atypical presentations are being noted [1]. Due to the development of widespread resistance to conventional drugs, several new drugs and other modalities of treatment have been developed and the conventional drugs are being tried in modified dosages with variable success.

Diagnosis

The mainstay of diagnosis is the demonstration of Leishman-Donovan (LD) bodies using Geimsa or other Ramonowsky stains. However, its positivity in different body tissues varies i.e. splenic aspirate (95%), buffy coat (90%), bone marrow aspirate (85%), hepatic aspirate (75%) and lymph node aspirate (60%). Culture of parasite in Novy-McNeil-Nicolle (NNN) medium or hamster inoculation takes time and is not usually practicable. Immunological tests are increasingly used in the diagnosis of kala azar and some of them are as follows :

a) Indirect fluorescent antibody (IFA) test using amastigote or promastigote antigens. This test remains positive even 12-15 years after cure has been achieved [4].

b) Direct agglutination test using promastigote antigen.

c) Detection of anti-66 kDa antibodies in a microenzyme linked immunosorbent assay (ELISA) is highly sensitive and specific in confirming kala azar [5].

d) Indirect haemagglutination and immunoblot

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testing [6].

e) Monoclonal antibody spot test is a simple test which is more sensitive than bone marrow smear examination [7].

f) Amplification of kinetoplast DNA using polymerase chain reaction is a highly sensitive test [8].

g) Detection of 72-75 kDa and 123 kDa fractions of Leishmania antigen in urine may be used to diagnose kala azar [9].

These tests are particularly useful for diagnosis in subclinical infections and in population screening as they are more sensitive and specific than the conventional aldehyde test. Antinuclear antibodies and low titres of anti ds-DNA antibodies may be present in occasional cases of kala azar leading to diagnostic confusion [10].

Criteria for cure

Clinical cure : When there is abatement of fever, gain in weight, rise in Hb content and WBC count with regression of splenic size by more than 60 per cent, it is termed as clinical cure.

Parasitological cure : Absence of the parasite in splenic puncture (SP) or bone marrow (BM) aspirates at the end of therapy.

Apparent cure : Clinical and parasitological cure at the end of therapy.

Full cure : Persistence of clinical and parasitological cure at the end of 6 months follow-up.

Treatment

The aim of treatment in kala-azar is killing of the parasite with effective drugs which are cheap and less toxic. Pentavalent antimonials are the first line drugs and pentamidine and amphotericin B are the second line drugs. Recently the latter are being used as first line drugs also [12]. Unfortunately the treatment of kala azar is complicated by a high incidence of drug resistance. There are approximately quarter of a million cases of kala azar in Bihar alone which are resistant to sodium stibogluconate (SSG).

Pentavalent antimonials

They act by inhibition of glycolysis and fatty acid oxidation in the parasite. One of these compounds, ureastibamine, was first made in India by Brahmachari and was probably the most used of this class of compound earlier in this century [10]. The preparations now available are sodium stibogluconate and meglumine antimonate. In the 1980 epidemic, it became clear that the traditional doses of stibogluconate (10 mg/kg body weight daily for six days) was inadequate. The dose recommended by WHO in 1984 was 20 mg/kg body weight per day with a maximum of 850 mg/day for 20 days and double the duration in relapse cases. The drug is now recommended to be used in the above dose with no upper limit for a minimum period of 30 consecutive days [11].

Pentamidine

It is a polyamine which acts by inhibition of kinetoplast DNA function. It is used in cases resistant to antimonials in a dose of 4 mg/kg body weight per day IM or slow IV on alternate days. The resistance to pentamidine was first reported in the 1991 epidemic and is now on the increase. In the earlier part of the present epidemic, 10-12 injections were shown to produce a cure rate of 98.8 per cent with no relapses. Recent studies have shown that even 20-33 injections may be followed by relapse [2]. It's side effects include hypoglycaemia, transient hyperglycaemia, permanent insulin dependant diabetes mellitus and cardiac arrhythmias.

Amphotericin B

Amphotericin B is an antifungal drug. It acts on the amastigotes by inhibiting sterol synthesis which leads to increased membrane permeability. It was initially used in a dose of 0.5 mg/kg body weight IV on alternate days for a total of 14 infusions. This dose was observed to be effective and non-toxic but was associated with high relapse rate. High dosage schedule using a total cumulative dose of 1 to 3 g though effective was found to be toxic. The dose now recommended is 0.75 mg/kg body weight on alternate days for a total of 15 infusions [12]. It is used in patients resistant to antimonials [13] and pentamidine [14] and in HIV positive cases [15]. Its major side effects are fever, chills, thrombophlebitis and nephrotoxicity.

Other drugs

Allopurinol, a xanthine oxidase inhibitor, is used in combination with antimonials in a dose of

50 mg/kg body weight/day for 4 weeks or more. Its role is limited as an adjuvant to antimony compounds.

A combination of sulphadiazine, trimethoprim and metronidazole given orally for 12-25 weeks has also been found to be effective in a recent study [16]. Tinidazole can be used instead of metronidazole in pregnant patients.

Roxithromycin, administered orally in a dose of 300 mg twice daily for 21 days, was found to be as effective as sodium stibogluconate [17].

Sodium aurothiomalate 10 mg initially followed by 20 mg IM on alternate days to a total of 250 mg has also shown good clinical responses [13].

Aminosidine, an aminoglycoside used in a dose of 15 mg/kg body weight is promising.

Ketoconazole acts by disrupting cell membrane of the parasite and has been used in kala azar with promising results [18]. Fluconazole may prove to be a suitable alternative.

INH, rifampicin, fluoroquinolones and clofazamine are also some of the drugs which have antileishmanial activity.

Levamisole is a immunomodulator and in combination with sodium stibogluconate may be of beneficial value.

New strategies

Recombinant human gamma interferon (IFN-gamma) acts by activation of infected macrophages, modulation of cell surface molecules, induction of secondary cytokines and enhancement of cytotoxic activity of NK cells and T lymphocytes. It was used in a dose of 100 micrograms/m2 body surface area subcutaneously for 30 days along with sodium stibogluconate. It resulted in early parasitic clearance, decreased duration of antimony therapy and 70 per cent cure in drug resistant cases [19].

Liposomal entrapped antileishmanial drug is directly delivered to the reticuloendothelial system, thus killing the amastigotes. This results in greater efficacy with fewer side effects. Liposomal drug preparations of sodium stibogluconate, amphotericin B and pentamidine are being evaluated for treating leishmaniasis. With this new system, the duration of drug therapy is expected to be brought down to only 3 days [2].

WR 6206 an orally administered primaquine analogue is in early phases of clinical trials. Recombinant human granulocyte- macrophage stimulating factor has been found to be effective in reversing neutropenia and reducing secondary infection in kala azar [21].

Kala azar and HIV Infection

Kala azar can occur at any stage of HIV infection. In more than half the cases kala azar occurs before the full blown picture of AIDS develops. There is an overall increase in the incidence of kala azar in HIV infected persons [15]. In one French study, it was observed that the incidence of kala azar was 100 times more in patients with CDC defining criteria of AIDS than in the general population [22]. Constellation of fever, splenomegaly and hepatomegaly was present in one fourth to one half of cases only. Splenomegaly was absent in approximately 40 per cent of the cases. In small number of cases none of the three classical clinical features were present. Atypical presentations include localised mucosal lesions in the alimentary tract (oral, oesophageal, gastric, intestinal), lungs, pleura, skin, and aplastic anaemia. Visceral disease may also occur with other leishmania strains (*L. tropica, L. infantum, L. braziliensis*) which are normally not associated with visceral disease in the immunocompetent individuals. Serological tests like indirect immunofluoroscence and ELISA are negative. In 50 per cent cases diagnosis is arrived at by the demonstration of the parasite in smears or by culture. Twenty five to fifty per cent of these patients do not respond to antimonials. Of those who respond, 50 per cent will relapse within a few months. Amphotericin-B is more effective and may prove to be the drug of first choice. Lipid associated formulations are also useful but are associated with a high degree of relapse [23]. Antimonials in combination with IFN may be used in severe or refractory cases. In a handful of HIV positive cases relapses have apparently been prevented by secondary prophylaxis with antimonials, allopurinol most convincingly with 2 weekly liposomal amphotericin B.

Current status of immunoprophylaxis and chemoprophylaxis, whether primary or secondary is not well defined. Ideal approach should be of

control of sandfly, treatment of patients and prevention of drug resistance.

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