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Kala-Azar - New Developments in Diagnosis and Treatment

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Abstract : Kala-azar is an endemic disease in many parts of India. Traditionally, diagnosis of this disease was based on demonstrating the parasites in various tissues like bone marrow or splenic aspirates. However, lack of high sensitivity of these methods led to the use of various immunodiagnostic methods in the diagnosis of kala-azar. Antigen detection and polymerase chain reaction to detect parasitic DNA have been found to be useful in patients with an underlying immunosuppressive disease like AIDS. For treating kala-azar, pentavalent antimonial compounds are still the first-line agents. However, due to increasing resistance to this agent, many patients at present require other drugs including amphotericin B and pentamidine. Toxic effects of these second-line agents have led to development of drug delivery systems like liposomal amphotericin B, which has shown uniform efficacy in clinical trials. Combining stibogluconate with either paromomycin or interferon-γ has also been shown to be useful in many patients with drug-resistant kala-azar. **(Indian J Pediatr 1999; 66 : 63-71)**

Key words : *Kala-azar; Visceral leishmaniasis; Direct aggluatination test; Pentavalent antimony.*

Kala-azar or visceral leishmaniasis (VL) is caused by protozoa belonging to the genus *Leishmania.* In India, *L donovani* is responsible for this disease. VL is widespread in tropical areas and has emerged as an opportunistic infection in HIV-positive patients. The incidence of HIV infection has been rapidly increasing in India, which may lead to increasing number of kala-azar patients. This makes rapid diagnostic and effective management strategies essential so as to reduce the burden of this disease. In this article, the newer methods of diagnosis and treatment of kala-azar have been discussed.

DIAGNOSIS OF KALA-AZAR

A diagnosis of kala-azar should be considered in patients who present with fever, anorexia, weight loss and discomfort in the left upper abdomen, and have pallor and splenomegaly. However, a definite diagnosis of kala-azar is based on the demonstration of the causative organisms in bone marrow or splenic aspirates, liver biopsies, or isolation of organisms in culture. These tests are invasive in nature, and collecting and processing these specimens require extensive facilities and experience. Further, the sensitivity of these techniques is low. The splenic aspirate detects around 70-90% active cases whereas bone marrow aspirate can detect only 50-75% cases. Therefore, immunodiagnostic tests have been studied by several workers which permit clinically conclusive, albeit indirect, diagnosis of VL. Several serologic tests have been developed to detect circulating antibodies to *L. donovani.* Tests have also been developed to detect circulating antigenic components

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of the parasite, or to detect the parasitic DNA in the tissue samples.

Immunodiagnostic Tests

Several immunodiagnostic methods have been developed which are less invasive and are useful in community surveillance studies. The skin test to demonstrate delayed-type hypersensitivity is positive only in patients with cured kala-azar. The present-day immunodiagnosis of kala-azar patients is based on various serologic tests that detect either antibodies or parasitic antigens.

Antibody detection : In patients with kala-azar, antibody production is vigorous and rapid. Various techniques of serodiagnosis of kala-azar are based on polyclonal stimulation of B-cell (non-specific tests) or clonal stimulation of B-cell (specific tests).

(a) *Non-specific tests :* Infection by *L. donovani* stimulates production of immunoglobulins by B-cell. In contrast, production of albumin is hampered leading to reversed albumin-globulin ratio. This increased production of immunoglobulins is used quite frequently at less-equipped, peripheral laboratories. Some of these tests are Napier's aldehyde test and Chopra's antimony test[1]. These tests are easy to perform but have a high false-positive rate due to overproduction of immunoglobulins in many other diseases. Since these tests fail to detect cases of early leishmaniasis, the sensitivity of these tests is around 85% only.

(b) *Specific tests :* Specific serological techniques are based on the demonstration of antibodies produced against the circulating parasitic antigens. The specificity of various tests depends on the antigen or its epitome used in the test, as the parasite will stimulate several antibody-producing B-cells including group and genus-specific (polyclonal) as well as species-specific (monoclonal) cells. Therefore, the sensitivity may depend on the test and its methodology but the specificity will depend on the antigen rather than the method used.

The conventional methods used for antibody detection include gel diffusion, complement fixation test (CFT), indirect hemagglutination test (IHA), indirect fluorescent antibody (IFA) test, and counter current immunoelectrophoresis (CIEP). However, besides practical difficulties at peripheral centres, the sensitivities and specificities of these tests are poor.

Direct agglutination test (DAT) is a promising test as it is simple, quick, cheap and specific and can be applied in the field conditions. Allain and Kagan first described DAT for the diagnosis of visceral leishmaniasis[2]. It was later modified and simplified to increase its sensitivity and specificity[3]. Since then, this test is being used widely in India and other endemic countries for diagnosis of VL[4-6]. In this test, the trypsinized whole promastigotes are fixed in formalin and then stained with a vital dye. Serum from a suspected case of kala-azar is incubated with the antigen and antigen-antibody agglutination is observed the next day. This test has been found to have a sensitivity of 96.5-100% and specificity of 91-95%. It has also been shown to be highly sensitive and specific in the early diagnosis of kala-azar patients[7]. The draw back of this test is that it remains

positive for more than 5 years after complete cure of the patient.

Enzyme-linked immunosorbent assay (ELISA) has also been used in the diagnosis of kala-azar. Several antigens have been used to enhance the specificity of this test. Cytoplasmic antigen has the advantage of being cheap and easy to prepare[5,8]. This antigen is coated on to the ELISA plates. The sensitivity of ELISA using soluble cytoplasmic antigens is nearly 100%, but specificity is not very high as cross-reaction with sera from patients with tuberculosis and toxoplasmosis has been recorded. If selective antigens (116 kDa, 72 kDa and 66 kDa) are used, the specificity could be as high as 100% but the sensitivity may go down to as low as 37.5%.

Another method, dot-ELISA has been developed in which interpretation can easily be made by visual inspection of reaction end points, obviating the need for ELISA reader[10]. A study comparing DAT and dot-ELISA has shown both of these tests to be of comparable diagnostic values, the former being more specific[11]. Besides, DAT does not require high technical skill and is cheap.

Since ELISA method is costly, ready-to-use dipstick ELISA has been developed and is under field trial in India and other countries. A latex agglutination test has also been developed using recombinant K39 antigen which takes only 10 minutes to perform the test. Both these tests have been shown to be highly sensitive and specific. The latex agglutination test has been found to be cost-effective and quick test which is suitable for field studies[5]. Indirect immunoperoxide assay (IPA) is a newer version of ELISA which requires a light microscope, and is highly sensitive and specific[12].

Another specific method of diagnosis is the western blotting. The promastigotes of *L. donovani* are grown to log phase, lyzed and the soluble proteins or recombinant protein is run on sodium dodecyl-sulphate-polyacrylamide-gel-electrophoresis (SDS-PAGE). The separated proteins are electroblotted onto a nitrocellulose membrane and probed with the test serum. If antibodies against specific antigens are present in the serum, they will bind to the specific band that can be visualized using anti-human antibody. With this method, minor antigenic differences among various organisms can also be detected. However, this test is very time-consuming, technically cumbersome and costly.

Antigen detection : Diagnosis of kala-azar by detecting specific antigen is considered to be more specific than antibody detection. The conventional method of antigen detection is known as reverse western blotting. Semi-quantitative dot-enzyme immunoassay (EIA) has also been used to demonstrate the antigens of parasitic origin in the circulation of patients with kala-azar[13]. The antibodies used in the detection of circulating antigens include antisera against the circulating antigens and monoclonal antibodies against *L. donovani* promastigotes[14]. The antibodies may detect antigens by competing with peroxidase-labelled promastigote soluble antigen, or by precipitating and dissociating antigen-containing circulating immune complexes. dot-ELISA has been shown to be sensitive in detecting geographically heterogeneous kala-azar patients. Antigen detection methods are useful when antibody production is impaired as in patients with HIV infection. Some workers have demonstrated the antigen in body fluids like saliva and urine,

which, in future, can obviate the need for venipuncture. A study from Spain has shown detection of two polypeptides fractions of 72-75 kDa and 123 kDa in the urine of patients with VL to have a sensitivity of 96% and specificity of 100%. Besides these antigens were not detectable after 3 weeks of treatment, suggesting a very good prognostic value[15].

DNA Detection Methods

The direct demonstration of parasites in various tissues is the most specific method but it lacks high sensitivity. The various antibody detection methods are highly sensitive but their specificity is not 100%. Further, these tests remain positive for several years, making diagnosis of relapses difficult. The antigen detection methods are highly specific but lack high sensitivity, and are technically cumbersome and costly. Also, for species identification, the parasites need to be cultured in good amounts. The method of polymerase chain reaction (PCR) has recently been used in the diagnosis of kala-azar. In this method, targeted DNA is amplified into millions of copies within a few hours which can then be detected. The pre-requisite for this technique is that the sequence of DNA to be detected should be known for that species. Initial few base pairs (18-30) of the targeted DNA and its complimentary DNA (cDNA) are synthesized. These fragments (primers) are allowed to anneal with the targeted sequences followed by DNA synthesis. The most commonly used primer sets for the diagnosis of kala-azar are 13A and 13B primers which are *Leishmania* genus specific[16]. The advantage of this technique is that sufficient amount of DNA can be produced from a single amastigote which can then be separated by electrophoresis. The sensitivity of detection can be enhanced using the radioactive probes which can be species or even strain specific.

Miscellaneous Tests

Recently, Sharma *et al* have reported the presence of 9-O-acetylated derivatives of sialic acid (9-O-ACSA) on the erythrocytes of patients with kala-azar using a rapid and inexpensive hemagglutination assay[17]. This test can be performed with minimal laboratory facilities. Achatinin$_H$, a lectin isolated from the hemolymph of a snail, binds exclusively to 9-O-ACSA derivatives, normally absent on human erythrocytes. Importantly, 9-O-AcSA derivatives are absent on erythrocytes of patients with malaria, tuberculosis and healthy controls from endemic and non-endemic areas.

TREATMENT

The objectives of treating kala-azar should be to cure the patient of intracellular parasites, prevent relapse and keep the costs to a minimum. Clinical relapse of kala-azar usually occurs within 6 months after completion of therapy. If relapse occurs, patients should be treated again with an antimonial. If the response is not satisfactory, or in case of primary unresponsiveness, other drugs should be used. These drugs are required in many patients due to increasing drug resistance and treatment failures reported from India[18].

Pentavalent Antimony

In India, sodium antimony is the most commonly available preparation of pentavalent antimonials. The WHO recom-

mends a dose of 20 mg/kg with a maximum dose of 850 mg for 20-40 days. However, the response rates have been reported to vary from 60% to 70%[18,19]. In India, there are pockets of drug resistance of high level as evidenced by failure rates as high as 80-90%.

The maximum dose of 850 mg/day has been recommended by the WHO; however, studies do not favour this[20]. There is data to suggest that a regimen of 20 mg/kg/d without an upper limit is more effective and not more toxic than the lower doses. The total dose should not be divided into two parts to be given twice a day as this may result in higher failure rates. It is recommended that antimony should be given for one month initially. If parasitic cure is not achieved in one month, but there is a significant reduction in the parasitic density, antiomy should be continued with weekly electrocardiography. If there is no significant reduction in parasitic density after one month of treatment, therapy should be switched to another agent.

Increase in the duration of treatment to 40 days before performing a bone marrow to assess the parasitic response has been suggested by some workers but this may lead to increased incidence of antimony-induced cardiac toxicity[20]. Transient flattening and/or T wave inversion may occur in many patients on antimony treatment. However, prolongation of corrected QT (QTc) interval, significant arrhythmias and concave depression of ST segment are indications to stop the treatment.

Pentamidine

Pentamidine is a diamidine compound whose antileishmanial activity is probably due to its interaction with parasitic DNA or nucleotides and their derivatives. Pentamidine isethionate is given parenterally by intramuscular injection or by slow infusion in single daily dose of 4 mg/kg body weight on alternate days. Initially, successful treatment in almost all patients was usually reported with 10-15 injections. However, studies conducted in the early 1990s have indicated a response rate of only 75% after 15-20 injections of pentamidine. Therefore, if parasites are still demonstrated in a tissue aspirate after 20 days of therapy, resistance to pentamidine should be considered.

Common side effects of pentamidine include impaired renal function, abnormal liver functions, hyperglycemia, hematological distrubances, skin rashes and hypoglycemia. Local reactions at the injection site such as pain and abscess formation have been reported in 18.3%, and immediate side effects such as hypotension in 9.6%. Diabetes mellitus can develop in some patients treated with pentamidine. Because of high incidence of side effects, the use of pentamidine in the treatment of kala-azar has been declining.

Amphotericin B

Amphotericin B, an antifungal agent, inhibits the sterol synthesis in amastigotes and is an effective drug for the treatment of kala-azar. It is usually used as a second line agent in treatment of kala-azar where stibogluconate has failed. This drug is given as infusion in a dose of 0.1-0.2 mg/kg on the first day. This dose is gradually increased by 0.1-0.2 mg/kg until a dose of 0.5-1.0 mg/kg/d is reached. The drug is given daily or on alternate days till a total dose of 20 mg/kg is achieved. Some authors recommend the therapeutic dose

from the beginning instead of increasing the dose over a few days. The drawbacks of amphotericin B are its high cost and side effects which include electrolyte imbalance, particularly hypokalemia, renal impairment and cardiac toxicity. Minor side effects like fever, rigors and vomiting are common. Careful monitoring of renal functions and electrolytes is required during treatment with amphotericin B.

Liposomal Drug Delivery System

The most exciting development in the treatment of kala-azar has been the development of various drug delivery systems. Liposomes are phospholipid vesicles that are engulfed by the cells of the reticuloendothelial system, resulting in direct delivery of the bound drug to the target cells and hence reduced side effects. Three lipid formulations of amphotericin B are presently being employed in clinical trials of patients with kala-azar. The commercially available liposomal preparation of amphotericin B (AmBisome®) has been used in a dose of 50 mg/d in patients with refractory kala-azar[21]. Presently, it is recommended in a dose of 3 mg/kg/d for 5 days followed by the same dose on days 14 and 21. In immunocompromised patients, it is administered in a dose of 3 mg/kg/d for 5 days and then 4 mg/kg/d on days 10, 17, 24, 31 and 38. Nephrotoxicity has been reported in about 19% cases compared with 34% of patients who receive the conventional drug. Infusion-related fever and chills are seen in 17% and 18% cases respectively, as compared to 44% and 54% with conventional drug. The cost of 50 mg of this preparation is nearly Rs. 11,000.

The second compound, amphotericin B cholesterol dispersion (Amphocil®) consists of cholesterol sulphate and amphotericin B (1 : 1 molar ratio) in disk-shaped particles and has been used successfully in patients with kala-azar. No serious side effects except fever and chills have been recorded. The mean time for the decline in fever was only 4.2 days which was much shorter than the conventional drug[22]. The third preparation is amphotericin B lipid complex of ABLC (AmBiosome®) which is administered in a dose of 3 mg/kg/d for 5 days as infusion[23]. Recent trials conducted in India have shown a dose of 2 mg/d for 3-5 days to be effective in most patients with refractory kala-azar[24].

Paromomycin

Paromomycin or aminosidine is active against Leishmania parasite. It has been used either alone or in combination with antimony. It is administered in a dose of 12-15 mg/kg for 20 days. Side effects include nephrotoxicity and ototoxicity. In a trial from India, combination therapy with stibogluconate and paromomycin for 20 days was successful in 75% cases of kala-azar[25].

Imidazole Derivatives

Ketoconazole and fluconazole have been used in the treatment of VL. These agents inhibit lanosterol demethylation leading to reduction of ergosterol, an essential component of parasitic cell membrane. Ketoconazole was initially used in patients with cutaneous leishmaniasis with encouraging results. This led us to use ketoconazole in patients with kala-azar. The initial results on a small number of adult patients using ketoconazole in a dose of

600 mg/d for 4 weeks were encouraging[26]. A randomized trial comparing sodium antimony gluconate with ketoconazole was conducted in 180 patients which showed cure rate with ketoconazole to be around 33%[27]. The most important advantage of ketoconazole is its availability as oral formulation and hence its utility in peripheral areas. This led other workers to use fluconazole (5 mg/kg/d) in patients with VL. However, overall, imidazoles appear to have some anti-leishmanial activity which could be used in combination with antimonials as first line therapy in areas where resistance to antimonials is high.

Cytokines

It is believed that resistance of the leishmanial parasite to various drugs is due to a failure of some critical element in the cellular immune response against the parasite. Various cytokines play a central role in mediating these responses. Interferon-γ (INF-γ) is a lymphokine that activates macrophage to destroy a variety of intracellular parasites, including leishmaniasis. In patients with kala-azar, a reduced secretion of interleukin-2 and INF-γ has been shown. These cytokines are essential for the activation of macrophages and ultimately, elimination of intracellular parasites. IFN-γ has been shown to augment the capacity of macrophages to eliminate the parasites and act synergistically with antimonials. It has been used in a dose of 100 μg/m^2/day subcutaneously for one month. The most common side effect is fever that can be controlled with anti-pyretics. In untreated patients of kala-azar, combinations of INF-γ and stibogluconate reduces the duration of antimony therapy, with higher cure rates[19]. In patients with multidrug-resistant leishmanial infection, cure has been reported in as many as 69% cases[28].

Miscellaneous Drugs

Allopurinol, an oral agent, has been used in a dose of 4-12 mg/kg in three divided dosages for 14-31 days. However, it has not been shown to be very useful in the treatment of kala-azar. Similarly, both isoniazid and rifampicin, either alone or in combination, have been demonstrated to be ineffective in the treatment of VL. WR 6026, a primaquine analogue, has been found to have high anti-leishmanial activity in animal models. However, the results of human trials are not very encouraging.

Conclusion

Serological test for detecting antibodies to Leishmania are the easiest and most efficient screening procedures; however, none of them is sufficiently specific to be diagnostic. Further in patients with HIV infection, anti-leishmanial antibodies may not be detectable, giving false negative results. In such situations, parasitic antigen and DNA detection methods are extremely helpful. For therapy of kala-azar patients, pentavalent antimonial compounds have been found to be ineffective in a large number of patients. More and more patients of VL require second-line agents for treatment, which however, have several serious side effects. Drug-targeted delivery system and cytokines hold the key to treatment of drug-resistant cases in future.

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EFFECT OF DRUG THERAPY ON LONG-TERM OUTCOME OF ASTHMA

There is an increasing notion that earlier intervention with inhaled corticosteroids as first line therapy might avoid possible irreversible airway obstruction and hence favourably alter the natural history of asthma.

One hundred seventy - five children with varying severity asthma were followed in an allergy clinic for 2 to 16 years. Children with moderately severe asthma were begun on cromolyn, and were switched to inhaled corticosteroids if this treatment did not control disease. A retrospective review was performed on chart of patients followed at least 6 months and for whom at least 2 years had passed since their first visit to the clinic. Spirometry was obtained at the end of the study and a questionnaire was completed. Original evaluations had included allergy testing in most cases, patient education, environmental control, etc.

Between treatment differences favoured both anti-inflammatory therapies over prn bronchodilators, with symptoms, emergency room visits, and hospitalizations all being significantly reduced. Spriometry improved in the anti-inflammatory therapy groups only. Delay in the therapy (defined as the interval between the first visit and start of anti-inflammatory therapy) suggested an unfavourable outcome for cromolyn but not inhaled corticosteroids. Treatment with cromolyn sodium or inhaled corticosteroids improves long-term prognosis of asthma. Earlier introduction of nonsteroid anti-inflammatory agents could further improve clinical outcomes. It can be inferred that patients with moderate-to-severe disease had more room for improvement and a long-term study using anti-inflammatory agents in *mild* asthma is needed.

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