

Review Article

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Childhood visceral leishmaniasis

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Visceral leishmaniasis (VL) is caused by the protozoan parasite *Leishmania donovani* and transmitted by the bite of infected sandfly *Phlebotomus argentipes*. Nearly half of the VL cases occur in children (childhood or paediatric VL). The clinical manifestations of childhood VL are more or less same as in the adults. Prolonged fever with anorexia and loss of appetite are the major presenting features. Marked enlargement of the spleen and liver (spleen larger than liver) with moderate to severe anaemia and changes in hair take place. Bacterial infection is a common co-infection and intestinal parasitic infestations are very common in children with VL. Liver function tests, blood, urine and stool may show abnormalities. Confirmation of diagnosis is made by demonstration of parasite by microscopic examination and culture of materials obtained by bone marrow aspiration or splenic puncture. Sodium antimony gluconate (stibogluconate) has been the drug of choice for over past 50 yr. Pentamidine isothionate, though effective is relatively toxic. Amphotericin B is the most effective drug for the treatment of VL. Miltefosine is the first-ever oral drug, is highly effective. Post kala-azar dermal leishmaniasis (PKDL) in children poses a therapeutic challenge. In the absence of an ideal vaccine for VL, control measures would essentially include prevention of transmission through vector control and community awareness.

Key words Childhood VL - clinical features - miltefosine - sodium antimony gluconate

Visceral leishmaniasis (VL) is caused by the protozoan parasite *Leishmania donovani* and transmitted by the bite of infected sandfly *Phlebotomus argentipes*. Nearly half of the VL cases occur in children (childhood or paediatric VL).

Clinical features

The clinical manifestations of childhood VL are more or less same as in the adults. Prolonged fever with anorexia and loss of appetite are the major

presenting features. Marked enlargement of the spleen and liver (spleen larger than liver) with moderate to severe anaemia, pancytopenia and hair changes occur. Cough and haemoptysis may be due to co-infection of pulmonary tuberculosis. Bacterial infection (pneumonia, septicaemia, otitis media, urinary tract infections and skin infections) is a common complication. Bacterial superinfection is one of the major complications leading to death in children with VL. Parasitic infestations of the gut are very common in paediatric VL patients.

Epidemiology

Global estimate: The global estimates for the incidence and prevalence of kala-azar cases per year are 0.5 and 2.5 million, respectively¹. More than 90 per cent of the world's VL cases are in India, Bangladesh, Nepal, Sudan and Brazil. The incidence of kala-azar in India is among the highest in the world^{2,3}.

Indian situation: VL has been one of the major health problems in the State of Bihar in India, for the past three decades or more. At present, 28 of 37 districts are endemic. Ninety per cent of all the cases in India are reported from Bihar State alone. VL is also being reported from several districts of West Bengal and Uttar Pradesh (adjoining Bihar). Bihar, being the second most populous and poorest State in India, has reported as many as 200,000 deaths from kala-azar so far. The adjoining low lying alluvial regions of Nepal-Bihar border are endemic zone for VL. In India, the calculated DALYs (disability-adjusted life years) lost due to kala-azar in 2002 were 19433 of which, nearly 50 per cent occur among children⁴.

The vector and disease transmission

The species of phlebotomine sandflies, which spread the disease, become infected by biting infected animals (*e.g.*, rodent or dog) or man. Since sandflies do not make noise when they fly, children may not realize that they are present. Sandflies are very small and may be hard to see; they are only about one-third the size of typical mosquitoes. They are usually most active in twilight, evening, and night hours (from dusk to dawn) and less active during the hottest time of the day. However, they will bite if they are disturbed, such as when children brush up against the trunk of a tree where sandflies are resting. Rarely, leishmaniasis is spread from a pregnant woman to her baby. Blood transfusions or contaminated needles also can spread the disease⁵.

Diagnosis

A presumptive provisional clinical diagnosis is made on the basis of presenting clinical features and history of living in an area endemic for VL. Routine

blood examination reveals leucopenia, moderate to severe anaemia and thrombocytopenia. Urine examination may reveal mild proteinuria. Stool examination may reveal presence of ova, cyst or different intestinal protozoa or helminths.

Liver function tests may show hypoalbuminaemia, normal or mild hyperbilirubinaemia with or without raised liver enzymes like serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and alkaline phosphatase. Serum urea and creatinine levels are usually normal.

Aldehyde test, although nonspecific and discarded, is strongly positive after 3 months. The new and simple rK39 diagnostic kit may be useful screening test^{6,7}. Confirmation of diagnosis is made by demonstration of parasite by microscopic examination of materials obtained by bone marrow aspiration or splenic puncture. Splenic puncture is safe in expert hands and when the prothrombin time is within normal limits. Promastigotes may be demonstrated by culture of material obtained by bone marrow aspirate or splenic puncture or blood culture in Novy-MacNeal-Nicolle (NNN) medium.

Treatment

Sodium antimony gluconate (stibogluconate) has been the drug of choice for over past 50 yr. Initially the dosage was 10 mg/kg per day deep im for 7 days. With the appearance of significant unresponsiveness to the drug, the currently recommended dosage is 20 mg/kg body weight per day for 30 days. Recently, resistance to antimony preparations has been reported to be about 50-60 per cent, and a number of toxicities including fatal cardiac toxicity have been observed⁸⁻¹⁰.

Pentamidine isothionate, though effective is relatively toxic. The dosage is 3 mg/kg body weight per day given slowly intravenous on alternate days for 5 doses. About 10 per cent of patients treated with the drug have been reported to develop irreversible diabetes mellitus. This drug is available in Bihar only through governmental sources¹¹.

Amphotericin B in a dosage of 1 mg/kg per day for 14 days is the most effective drug for the treatment of VL. The drug is required to be given by slow infusion over a period of 4 h on alternate days. Hypokalaemia and rigour are major side effects. Renal and ototoxicity have also been observed. The drug is costly and patients are required to be hospitalized^{12,13}. Amphotericin B lipid complex (Ambisone) is highly effective in a single dose but the drug is prohibitively costly¹⁴.

Miltefosine is the first-ever oral drug developed for the treatment of new and resistant cases of VL. Miltefosine is highly effective (>95% final cure rate). The dose of the drug is 2.5mg/kg body weight per day in 2-3 divided doses for 28 days. Side effects include mild diarrhoea and vomiting. The drug has been licensed in India and Germany. Miltefosine is now considered to be the first line of drug of choice for the treatment of VL in children¹⁵⁻¹⁸.

Paramomycin 15 mg/kg body weight per day for 21 days has recently been found to be highly effective for the treatment of VL in adults and has to be administered by the intramuscular route. The efficacy of the drug in children is yet to be demonstrated¹⁹.

Post kala-azar dermal leishmaniasis (PKDL) in children poses a therapeutic challenge. It is generally treated by prolonged courses of stibogluconate or amphotericin B. The dose and duration of such treatment are yet to be standardised. Effectiveness of miltefosine and paramomycin with their dosage and duration of treatment remains to be studied by carefully planned controlled clinical trials.

Combination of two or more drugs particularly for the treatment of VL and PKDL is an attractive proposition, and is expected to reduce the duration and toxic side effects of therapy and may also minimize the cost. However, combinations which would be synergistic in their actions, supported by pharmacokinetic data, require to be studied in well-designed human trials.

Prevention and control strategies

Since VL is a chronic disease and results in a lot of hardship on the part of the children and their parents, prevention and control strategies are the best solution. In the absence of an ideal vaccine for VL, control measures would essentially include prevention of transmission through vector control and community awareness²⁰.

However, despite efforts made to achieve disease control, the transmission goes on unabated spreading to new areas, which were earlier considered non endemic. Risk factors like poverty, malnutrition, illiteracy, and behavioural and ecological conditions are some of the important determinants of VL affecting the poor population. The health facilities at peripheral level are inadequate to cater to the needs of the community. As a result, the poor people depend on local quacks for treatment. When treatment by these quacks fails to give relief or cure, the people go with their children to big cities for treatment. Such treatment being expensive, they are forced to sell their property, other belongings or even their houses. Thus, this disease aggravates poverty.

Vector (sandfly) plays an important role in disease transmission. High incidence of VL is reported during pre-monsoon season that coincides with vector abundance and increased man-vector contact due to sleeping habits of children in open space in summer. The vectors are found in abundance in peridomestic vegetations around the households during the period, which are usually not covered by insecticide spray operation. Resistance to DDT by the vectors is also a matter of concern.

Community awareness and participation act as fulcrum in sustainability of any successful community programme. Studies undertaken on community awareness of kala-azar and PKDL revealed poor knowledge of disease transmission, vector habitats, use of impregnated bed nets and occurrence of PKDL²¹. Low acceptance of DDT spray leads to inadequate coverage. Social stigma related to macular and nodular skin lesions of PKDL leads to low case identification and treatment. Sandflygenic conditions like mud plastered houses, granaries

inside houses with cracks and crevices, inadequate light, bushes, vegetations especially bamboo trees in and around houses, heaps of cow dung stocks near living areas are prevalent in the areas from where most cases are reported. Better community awareness on disease causation, vector transmission and health seeking behaviour will help in making a change in the existing scenario.

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