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Diagnosis of Leishmaniasis in Children

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1. Introduction

Leishmaniasis, a group of protozoan diseases caused by *leishmania* parasites, is transmitted by the bite of some species of sand fly. This affects various age groups depending on the infecting *leishmania* species, geographical location, and disease reservoir and host immunocompetence. [1] Leishmaniasis is estimated to affect 10-50 million people in endemic tropical and subtropical regions on all continents except Australia and Antarctica. [2] The prevalence is the highest in central and south America, southern Europe, central Africa, and parts of southern and central Asia. The extent and presentation of the disease depends on several factors, including the humoral and cell mediated immune response of the host, the virulence of the infecting species, and the parasite burden. Children are at greater risk than adults in endemic areas. Malnutrition contributes to the development of disease, and incomplete therapy of initial disease is a risk factor for recurrence of leishmaniasis. [1]

Localized cutaneous leishmaniasis (LCL) is caused by *L. major* and *L. tropica* in North Africa, the Middle East, central Asia, and the Indian subcontinent. *L. aethiopica* is a cause of LCL and diffuse cutaneous leishmaniasis (DCL) in Kenya and Ethiopia. Visceral leishmaniasis (VL) in the Old World is caused by *L. donovani* in Kenya, Sudan, India, Pakistan, and China and by *L. infantum* in the Mediterranean basin, Middle East, and Central Asia. *L. infantum* is also a cause of LCL (without visceral disease) in this same geographic distribution. *L. tropica* also has been recognized as an uncommon cause of visceral disease in the Middle East and India. In the new world, *L. mexicana* causes LCL in a region stretching from southern Texas through Central America. *L. amazonensis*, *L. pifanoi*, *L. garnbami*, and *L. venezuelensis* cause LCL in South America, the Amazon basin, and northward. Members of the Viannia subgenus *L. braziliensis*, *L. panamensis*, *L. guyanensis*, and *L. peruviana* cause LCL from the northern highlands of Argentina northward to Central America. Members of the Viannia subgenus also cause mucosal leishmaniasis (ML) in a similar geographic distribution. VL in the New World is caused by *L. chagasi* (now considered by the same organism as *L. infantum*), which is distributed from

Mexico (rare) through central and south America. Like *L. infantum*, *L. chagasi* can also cause LCL in the absence of visceral disease. [2]

The emergence of the leishmaniasis in new areas is the result of 1. Movement of a susceptible population in to existing endemic areas, usually because of agricultural or industrial development or timber harvesting; 2. Increase in vector and/or reservoir population as a result of agriculture development projects; 3. Increase in anthroponotic transmission owing to rapid urbanization in some focuses; and 4. Increase in sand fly density resulting from a reduction in vector control programs.

The cutaneous form of the disease is generally mild but may cause cosmetic disfigurement. Mucosal and visceral leishmaniasis is associated with significant morbidity and mortality.

2. Type of Leishmaniasis

Two forms of leishmaniasis; cutaneous and visceral are seen in humans. Some texts also distinguish a mucocutaneous form, while others consider it to be a subset of cutaneous leishmaniasis. The form of the disease and the usual clinical signs vary with the species of leishmania. Some infections remain asymptomatic.

- Cutaneous leishmaniasis (Figure-1)
 - Localized cutaneous leishmaniasis/oriental sore (LCL)
 - Diffuse cutaneous leishmaniasis (DCL)



Figure 1. Features of cutaneous leishmaniasis in children

- Mucosal leishmaniasis /Espundia (ML) (Figure-2)



Figure 2. Lesion in palate in Mucosal Leishmaniasis/Espundia (ML)

- Visceral leishmaniasis (Figure-3 & 4)



Figure 3. Hepatosplenomegaly in children of VL



Figure 4. Blackish appearance of skin in children of VL

2.1. Cutaneous leishmaniasis

2.1.1. Localized cutaneous leishmaniasis (LCL)

LCL can affect individuals of any age but children are the primary victims in many endemic regions. Most infections probably remain symptomless. [3] The first sign of an infection is typically a small erythema that develops after a variable prepatent period at the site where an infected sand fly has bitten the host. The erythema develops into a papule then a nodule that progressively ulcerates over a period of 2 weeks to 6 months to become the lesion that is characteristic of LCL. It typically presents 1 or a few lesions located on exposed skin, such as the face and extremities. Rarely >100 lesions have been recorded. Papule enlarges to 1-3 cm in diameter. The ulcers are usually non-tender, and surrounded by sharp, indurated, erythematous margins. There are no drains, unless a bacterial super infection develops. Lymphatic spread and lymph gland involvement, which may precede lesion development, [4] are common and there is a variable tendency for lesions to self cure within approximately 2-6 months e.g *L. major*, 3-9 months e.g *L. mexicana*, or 6-15 months e.g *L. tropica*, *L. braziliensis*, *L. panamensis* of disease onset. Regional lymphadenopathy and palpable nodules or lymphatic cords, the so-called sporotrichoid appearance is also more common when the patient is infected with organisms of the viannia subgroups [5, 6, 7, 8, 9].

Spontaneous healing usually results in lifelong protection from disease, which may or may not be restricted to the same *Leishmania* species. Resolution of disease results in a lifelong scar, which depending on its size and location may cause substantial trauma in affected individuals. [10]

2.1.2. Diffuse Cutaneous Leishmaniasis (DCL)

DCL is a rare form of leishmaniasis found in parts of south and central America, Ethiopia, and Kenya [11] It is caused by organisms of the *L. mexicana* complex in the New World, and *L. aethiopia* in the Old World. DCL manifests as large non-ulcerating macules, papules, nodules, or plaques that often involve large areas of skin and may resemble lepromatous leprosy. The face and extremities are most commonly involved. Dissemination from the initial lesions usually takes place over several years. It is thought that an immunologic defect underlies this severe form of cutaneous leishmaniasis. [2]

The broad clinical spectrum of cutaneous leishmaniasis makes diagnosis of present and past cases difficult. Differential diagnosis is important because diseases of other causes but with a similar clinical spectrum to leishmaniasis are common in leishmaniasis endemic areas.

Diseases that should be considered in the differential diagnosis of cutaneous leishmaniasis include sporotrichosis, blastomycosis, chromomycosis, lobomycosis, cutaneous tuberculosis, atypical mycobacterial infection, leprosy, ecthyma, syphilis, yaws, and neoplasms. [2]

2.2. Mucosal Leishmaniasis/Espundia (ML)

ML is an uncommon but serious manifestation of leishmanial infection resulting from hematogenous metastases to the nasal or oropharyngeal mucosa from a cutaneous infection. [2]

Mucosal leishmaniasis is most commonly associated with *L. braziliensis* thus it is usually limited to South America. Mucosal involvement is the most serious complication in *L. braziliensis* infections and can have disfiguring and life-threatening mucosal leishmaniasis in a varying proportion of patients. In most endemic areas, 1-10% LCL infections result in ML 1-5 years after LCL has healed, [12] but reports do exist for which ML presented at the same time as LCC [13] or for which up to 25 % of LCL infections resulted in ML. [14]

Patients with ML most commonly have nasal mucosal involvement and present with nasal congestion, discharge, and recurrent epistaxis. Oropharyngeal and laryngeal involvement is less common but associated with severe morbidity. Marked soft tissue, cartilage, and even bone destruction occurs late in the course of the disease, and lead to visible deformity of the nose around mouth, nasal septal perforation, and tracheal narrowing with airway obstruction. [2] ML never heals spontaneously, is very difficult to treat with secondary bacterial infections common, and is potentially fatal. [15]

Differential diagnosis of ML includes syphilis, tertiary yaws, histoplasmosis, paracoccidiodomycosis, sarcoidosis, Wegner granulomatosis, midline granuloma.

2.2.1. Investigation

Parasitological diagnosis remains the gold standard in cutaneous and mucosal leishmaniasis, because of its high specificity. It includes microscopic examination of Gimsa-stained biopsy smears or aspirates, histopathological examination of fixed lesion biopsies, or culture of biopsy triturates or aspirates. [16] Microscopic examination is probably the most common diagnostic approach used, because more sophisticated methods are expensive and rarely available at primary, secondary, and tertiary health care levels in endemic areas. Culture methods are probably the most informative, allowing species identification and characterization, but require a wealth of technical expertise, and are time consuming and expensive. The sensitivity of these techniques however, tends to be low and can be highly variable, depending on parasite number and dispersion in biopsy samples, technical expertise, and culture media. Molecular parasitological diagnosis for cutaneous leishmaniasis was developed extensively during the past decades and has been recently reviewed. [17] It is essentially done by PCR based methods and is particularly useful in cases with low parasite load such as mucosal leishmaniasis. Reported specificity is 100%, sensitivity is improved by 20-30% in LCL and 55-70% in ML, when compared with conventional parasitological diagnosis. There has been substantial effort in applying molecular diagnostics in the field (e.g successful detection of parasite DNA in blood or tissue smears; development of rapid PCR oligochromatography), its widespread use is still hampered by the requirement of substantial laboratory infrastructure, technical expertise, and cost. [17]

Serological diagnosis is rarely used in cutaneous or mucous leishmaniasis because of variable sensitivity and specificity. [18] The Montenegro skin test is occasionally used in diagnosis of

cutaneous disease (eg.in epidemiological surveys), because of its simple use and high sensitivity and specificity; [19] however, it fails to distinguish between past and present infections.

2.3. Visceral Leishmaniasis/ Kala azar (VL)

More than 90% 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. Male: female ratio of the disease is 2:1 in India. [20] VL is found in all age groups. In India and Brazil, an animal reservoir has not been identified. The epidemiological form of the disease was first described in India, and is known as the Indian type of visceral leishmaniasis. In this form of the disease, children between 5 and 15 years of age are affected. *L. donovani* is the predominant parasite of this form of leishmaniasis in India, while in the new world the disease is predominantly caused by *L. chagasi*. In Mediterranean basin, VL mainly affects children 1 to 4 years of age; it is caused mainly by *L. infantum*, transmitted by phlebotomic sand flies, and dogs are the most important reservoir. The African type of VL is again caused by *L. infantum* affecting older children and young adults and rodents are the reservoir hosts. [21, 22]

After inoculation of the organism into the skin by the sand fly, the child may have a completely asymptomatic infection or an oligosymptomatic illness that either resolves spontaneously or evolves into active Kala-azar. Children with asymptomatic infection are transiently seropositive but show no clinical evidence of disease. Children who are oligosymptomatic have mild constitutional symptoms (malaise, intermittent diarrhea, poor activity tolerance) and intermittent fever; most will have a mildly enlarged liver. In most of these children the illness will resolve without therapy, but in approximately ¼ it will evolve to active Kala-azar within 2-8 months. Extreme incubation periods of several years have rarely been described. During the first few weeks to months of disease development, the fever is intermittent, there is weakness and loss of energy and the spleen begins to enlarge. The classic clinical pictures of high fever, marked splenomegaly, hepatomegaly and severe cachexia typically develop approximately 6 months after the onset of illness; but a rapid clinical course over 1 month has been noted in up to 20% of patients in some series. At the terminal stages of VL the hepatosplenomegaly is massive, there is gross wasting, the pancytopenia is profound, and jaundice, edema, and ascities may be present. Anaemia may be severe enough to precipitate heart failure. Bleeding episodes, especially epistaxis are frequent. The late stage of illness is often complicated by secondary bacterial infection.

A young age at the time of infection and underlying malnutrition may be a risk factor for the development and more rapid development of active VL. VL has been increasingly recognized as an opportunistic infection associated with HIV infection.

In an African study, clinical symptoms on VL patients include fever 95.8%, weight loss 85.9%, abdominal pain 67.7%, Loss of appetite 56.3%, cough 39.4%, epistaxis 29.6%, joint pain 29.6%, diarrhea 25.4%. In the same study clinical signs of VL were splenomegaly (93%), pallor (83%), emaciation (76.1%), hepatomegaly (73.2%), lymphadenopathy (50.7%), oedema of lower limbs (14.1%), skin darkness (08.5%), ascitis (08.5%). [23]

Intermittent fever (95%), pallor (77%), refusal to feed or anemia (40%), weight loss (18%), abdominal distension (18%), cough (16%), vomiting (15%) and diarrhea (12%) were the commonest presenting complaints in a study in southern Greece. Massive splenomegaly (99%), hepatomegaly (85%), lymphadenopathy (39%), and echymoses or gingival bleeding (2%) were other common manifestations noted on physical examination. The investigators also reported certain unusual manifestations in the form of tachycardia (80%), cardiac murmur (75%), petechiae or echymoses (30%), and jaundice (20%). Abdominal distension was observed in 80% of their cases. [1]

The most common clinical features are anemia, fever, splenomegaly that presents in > 90% of cases in southern and northwest Iran. Hepatomegaly is less frequent than splenomegaly. Jaundice, edema, and ascitis are reported less frequently. It seems that all of signs and symptoms are compatible with Mediterranean type except for the absence of significant lymphadenopathy. [24]

In a series of seven Kala azar cases in children presented with jaundice, 42% were diagnosed clinically as chronic liver disease, 8% as congenital hemolytic anemia, and 50% as Kala azar. Kala azar may present with various clinical manifestation in children and adult. Jaundice can be considered to be a common manifestation particularly in pediatric Kala azar patients otherwise, it may mislead to another diagnosis if it is taken as rare feature. [25]

2.4. Post-Kala azar Dermal leishmaniasis (PKDL) (Figure 5)

A small percentage of patients previously treated for VL develop diffuse skin lesions, a condition known as post Kala azar dermal leishmaniasis. PKDL occurs in a very high percentage in the 0-9 years age group. [20] These lesions may appear during or shortly after therapy (Africa) or up to several years later (India). [2]



Figure 5. Nodular lesions in children of PKDL

This syndrome is characterized by a maculopapular, maculonodular rash around the mouth, which spreads. It commonly involves the face and torso. They may persist for several months or many years. [2] In India PKDL is seen in 1-3% of successfully treated cases of VL. [1] The clinical features of PKDL have remained almost the same over the years. [20]

The clinical picture of VL may also be consistent with that of malaria, typhoid fever, miliary tuberculosis, scistosomiasis, brucellosis, and leukemia. PKDL should also be differentiated from yaws, syphilis, leprosy, and muco-cutaneous leishmaniasis. [1, 2]

2.4.1. Investigation

Laboratory findings associated with classic Kala azar include anemia (hemoglobin 5-8 mg/dl), thrombocytopenia, leucopenia (2000-3000 cells/ μ L), elevated hepatic transaminase levels, and hyper globulinemia (> 5gm/dl) that is mostly immunoglobulin G (IgG). [2]

3. Demonstration (microscopy) and isolation of parasite (culture) (Figure 6)

Direct visualization of amastigotes in clinical specimens is the diagnostic gold standard in regions where tissue aspiration is feasible and microscopy and technical skill are available. [24] Microscopy of bone marrow aspirates is the safest diagnostic approach for paediatric patients, with amastigotes seen in more than 90% of cases by an experienced observer. The higher diagnostic efficacy of the bone marrow examination in children is probably related to the heavier parasitisation encountered in children. Microscopic examination of splenic aspirates offers the highest sensitivity (up to 98%), but is associated with the risk of life-threatening haemorrhage in cases with profound thrombocytopenia. [1] The results of culture in Novy-McNeal-Nicole (NNN) and RPMI 1640 media have been disappointing in one study. [24]

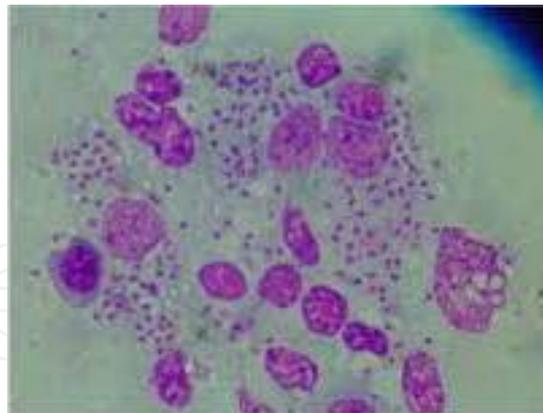


Figure 6. Amastigotes forms of *Leishmania spp* by Giemsa stain

4. Serological methods

Serological methods are highly sensitive and non-invasive. They are comparatively more suited for diagnosing VL in endemic regions. These methods are either based on detection of

antibodies (produced against parasite by polyclonal activation of B cells) or antigens. Many conventional methods for antibodies detection for instances, gel diffusion, complement fixation test, indirect haemagglutination test, indirect fluorescent antibody detection test (IFAT), and counter current electrophoresis have been evaluated with varying sensitivities and specificities.

Direct agglutination test (DAT) has been found to be 91-100% sensitive and 72-100% specific in various studies elsewhere in the world. [26]

Detection of anti-K39 by immune-chromatographic strip testing is a rapid and non-invasive method of diagnosing Kala azar. It entails a good sensitivity and specificity. In symptomatic patients, anti-K39 strip-test sensitivity is high (90-100%), while specificity might vary by region. [3]

Two urinary antigens of 72-75 and 123 kDa have been reported to be very useful in diagnosis and prognosis of Kala azar with sensitivity of 96% and specificity of 100%. [26]

DNA detection methods: a variety of nucleic acid detection methods targeting both DNA and RNA have been developed. The most suitable target for the DNA based diagnosis is kinetoplast DNA minicircle (K-DNA). The leishmania polymerase chain reaction (PCR) assays using peripheral blood as clinical specimen showed to be a highly efficient non-invasive alternative with sensitivity varying from 80-100%. [27]

The *Leishmania* skin test (LST): LST is a measure of delayed hypersensitivity to leishmanial antigen. The test remains negative through the period of active disease. The change from negative to a positive LST is regarded as a prognostic sign. [28]

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