Adances in the Diagnosis of Visceral Leishmaniasis

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Visceral Leishmaniasis (VL or Kala azar) is a disease of poor and neglected populations; it affects 79 countries of the world and accounts 58, 000 new cases to each year [1]. Indian subcontinent covers 90% VL cases of the world, among which Bihar state accounts for most cases [2]. In absence of antileishmanial vaccines early and accurate diagnosis holds the key for the control of VL. Till date parasitological method remains the gold standard for diagnosing VL. Microscopic demonstration of amastigotes in splenic aspirates, peripheral blood mononuclear cells and buffy coat has been shown to possess high sensitivities and absolute specificity [3,4]. Serology based diagnostic methods to detect antibodies against different recombinant Leishmania antigens (rK39, rK28, rK16) are also routinely employed to detect active cases in the field conditions. Out of these rK39 immunochromatographic test (ICT) remains the test of choice for clinicians because of its 100% sensitivity in VL subjects and 85-100% specificity in endemic healthy controls [5]. Recently recombinant antigen rK16, 39-amino acid protein obtained from C terminus of L. donovani immobilized in two different formats, a flow through test (KEFT) or Signal KA, and a lateral flow test (KELF) or Crystal KA had shown higher (sensitivity 93-99% and 99.5% respectively) in Indian subcontinent than East Africa and Brazilian VL subjects [6,7].

rK28 was designed to increase antigen epitope density from L. donovani hasp1 and rK39 kinesin gene. In ELISA, it has shown 100% sensitivity in VL subjects and 94% specificity in endemic healthy controls [6]. Antibody based detection methods have two major limitations. Although antibody titre level goes down after successful VL treatment, it still can be detected after many years. Secondly, house hold contacts from VL patient families have shown positivity for anti-leishmanial antibodies. Sero-prevalence in these individuals varies from 10-30% and they are termed as asymmetric cases. Therefore, antibody based approaches should be confirmed with other VL defining tools before treatment [8]. In order to develop non invasive diagnosis for VL, the strip tests have been evaluated using human saliva which is a good source of anti-leishmanial antibodies. Sensitivity for rK39 antigen using saliva was 83.3% and 82.5% in ELISA and ICT technique, whereas specificity was found to be 90.5% and 91.5% respectively by ELISA and ICT in endemic healthy controls [9]. A recent study from Bangladesh has shown satisfactory results with urine samples of VL patients and endemic controls with rK39 based ICT (93.3% specificity and 95% sensitivity) [10]. Since the reliability of these RDTs in any region depends upon the manufacturer, therefore quality and performance should be checked before implementing these RDTs for VL diagnostic algorithm. In immune-compromised patients (HV-VL co-infection) antibody titre is low therefore RDT’s should be evaluated properly in clinical settings to define VL subjects and treatment recommendations.

Antigen based diagnosis is more specific than antibody based methods because it can also be performed in the immune-compromised patients with low antibody titre. Two polypeptide fractions 72-74 kDa and 123 kDa were reported in the VL subject’s urine samples, first polypeptide had shown 96% sensitivity and 100% specificity and surprisingly these antigens were not detectable after successful treatment of VL subjects, which predicts very good prognostic value [11].

Molecular based methods for VL diagnosis have been developed and evaluated to overcome the limitations of parasitological (high invasiveness and non applicability to field conditions) and serological methods (low prognostic value). These methods are primarily based on qualitative PCR and involve amplifying parasite DNA in VL patient’s blood sample. Various regions of leishmania genome have been targeted (high copy number kDNA, small subunit of rRNA, ITS-1) to develop highly specific and sensitive primers [12]. Noninvasive samples like buccal swabs have also been evaluated using PCR and have been shown to give encouraging results [13]. More recently, quantitative PCR with its high sensitivity, shorter run times and reduced contamination risks has been introduced and currently being evaluated in clinical settings [14,15]. Another technology, Nucleic acid sequence-based amplification (NASBA) can be a better marker of active disease and cure as it involves amplification of specific RNA sequences [16]. The major thrust in molecular diagnosis of VL is now to improve the reproducibility and field applicability of PCR based methods. The introduction of Leishmania OligoC-Test and NASBA-Oligochromatography (OC) in dipstick format is a step forward in this direction. Both tests are available as self-containing kits and have shown high sensitivity and specificity in Sudan, Peru and Kenya [17,18].

Another advancement in molecular based detection is Loop mediated isothermal amplification which does not require sophisticated machinery, cold chain for storing reagents and positivity can be judged visually based on the turbidity of reaction mixture and therefore can have wide field applicability if developed further. A recent study from Bangladesh has shown encouraging results with LAMP with a diagnostic sensitivity of 90.7% and 100% specificity [19]. The laboratory diagnosis of VL has seen tremendous progress during the last decade and will definitely play an important role in VL elimination program by developing more rapid, sensitive, less expensive and non-invasive diagnostic procedures.

References


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