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# Human Atypical Trypanosomosis in Indian Subcontinent

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**Abstract**
Human trypanosoma infections as those seen in Africa and South America were unfamiliar in India till 1974. In Africa, the disease, known as human African trypanosomiasis (HAT) or sleeping sickness, is basically caused by *Trypanosoma brucei gambiense* (chronic form) or *T. b. rhodesiense* (acute form), whereas the American trypanosomosis (Chagas' disease), is caused by *T. cruzi*. Along with these parasites a number of atypical human infections caused by other *Trypanosoma* species (or sub-species) have been reported, namely *T. brucei brucei, T. congolense, T. evansi, T. vivax, T. lewisi,* and *T. lewisi*-like. Across the world 20 patients with atypical human trypanosomiasis were documented, eight were confirmed between 1974 and 2014 due to improved molecular diagnostic assays. However, the numbers of cases are atypical human trypanosomosis might be underestimated. Thus there is a need for the improvement and evaluation of new diagnostic tests. A further field investigation is most important for detection and confirmation of atypical cases. Here we have reviewed in brief the human atypical trypanosomosis in Indian Subcontinent.
**Keywords:** Human trypanosomiasis, *Trypanosoma evansi,* Indian Subcontinent.

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## Introduction

Trypanosomosis is caused by different species of unicellular eukaryotic haemoflagellate *Trypanosoma*. The parasites for human trypanosomosis were first discovered by David Bruce in 1895 and he suggested it to be the cause of Nagana disease in horses and cattle. Forde, in 1902, confirmed motile trypanosomes in the blood of a man suffering from fever. The parasite was afterward named *Trypanosoma gambiense* in the same year by J. E. Dutton as the patient was from Gambia. Previously these are the only two strains of trypanosome which are pathogenic to human beings i.e. *T. brucei* and *T. cruzi* [1]. There are only three reports of the accidental transmission of the *T. lewisi* like animal parasite to human beings in the South East Asia region excluding India. The first is a very old report way back in 1933 from Malaysia; [2] the second is from Thailand in 2005 [3] and the third from Gambia [4]; All these cases were infants suffering from febrile illness. The environmental conditions in India are conducive to the spread of the parasite from animals to human beings.

India has the distinction of being the country where the first two mammalian trypanosomes i.e. *T. lewisi* and *T. evansi* were discovered. The geographical area affected by enzootic trypanosomosis caused by non-tsetse borne *T. evansi* is about three times greater than caused by tsetse borne trypanosomes [1, 5]. The parasite causes severe pathogenesis in domestic, wild and laboratory animals [6]. India is thought to be the major source from where surra has spread within livestock throughout the continent of Asia and Islands of Indian Ocean [6]. Similarly, there was introduction of *T. evansi* from India to Australia when camels were exported from India to Port Hedland in 1907 [7]. Recently, the disease was introduced in France after the introduction of dromedary camels from a dromedary breeding farm in Canary Islands [8].

Economically important, pathogenic widely distributed mammalian trypanosome *T. evansi*, occurring in India, fails to infect humans due to innate immunity of the host [6]. Humans are resistant to infection with *T. evansi* and other related African trypanosomes except *T. brucei rhodesiense* and *T. brucei gambiense* because serum resistance-associated protein (SRA) gene is absent in this group of trypanosomes, which interacts specifically with apoL1 and neutralizes it. Furthermore human serum has an innate trypanolytic activity, first identified in 1900 by Laveran and Mesnil [9]. The protein accountable for this activity is a member of the serum apolipoproteinL (apoL) family, termed apoL1 [10]. This protein binds to a subset of high density lipoprotein (HDL) particles, which also contains another human protein, termed haptoglobin related protein (Hpr). Studies with *T. brucei* have shown that the parasites possess a precise surface receptor for capturing hemoproteins that are essential for the survival of the host oxidative response. This receptor also binds Hpr containing HDL particles; endocytosis of this receptor-lig and complex results in internalization of apoL1 [9]. Within the lysosome, apoL1, a membrane pore forming protein, is targeted to the lysosomal membrane, where, it persuades an influx of chloride ions from the cytoplasm resulting in osmotic imbalance and death of the parasite. The

**Table 1:** Cases of atypical human trypanosomoses [11, 15].

| Sr. no | Parasite | Place | Year | Method of diagnosis* |
|---|---|---|---|---|
| 1 | *T. vivax* | Ghana | 1917 | Blood smear examination |
| 2 | *T. b. brucei* | Pasteur Institute | 1930 | Blood smear examination |
| 3 | *T. b. brucei* | Congo | 1947 | Blood smear examination |
| 4 | *T. b. brucei* | Ethiopia | 1987 | Blood smear examination (blood incubation infectivity test) |
| 5 | *T. b. brucei* | Ghana | 2003 | PCR |
| 6 | *T. congolense* | Coˆ te d'Ivoire | 1998 | PCR |
| 7 | *T. evansi* | India | 1977 | Blood smear examination |
| 8 | *T. evansi* | Sri Lanka | 1999 | Blood smear examination |
| 9 | *T. evansi* | India, Seoni | 2004 | PCR |
| 10 | *T. evansi* | India, Kolkata | 2005 | Blood smear examination |
| 11 | *T. evansi* | Egypt | 2010 | Blood smear examination |
| 12 | *T. lewisi* | Malaysia | 1933 | Blood smear examination |
| 13 | *T. lewisi* | India, Parsda | 1974 | Blood smear examination |
| 14 | *T. lewisi* | India, Parsda | 1974 | Blood smear examination |
| 15 | *T. lewisi* | The Gambia | 2003 | PCR (Amplicons sequencing) |
| 16 | *T. lewisi* | Thailand | 2003 | PCR (Amplicons sequencing) |
| 17 | *T. lewisi* | India, Mumbai | 2006 | Blood smear examination |
| 18 | *T. lewisi* | India, Pune | 2007 | PCR |
| 19 | *T. lewisi* | India, Bagpat | 2010 | PCR (Amplicons sequencing) |
| 20 | *T. lewisi* | India, Madhya Pradesh (Chhindwara) | 2014 | PCR (Amplicons sequencing) |

parasites responsible for trypanosomosis are resistant to lysis by normal human serum [11]. Serum resistance is conferred by a variant surface glycoprotein termed serum resistance associated protein. SRA is a lysosomal protein, and the N terminal alphahelix of SRA interacts strongly with a carboxy terminal alphahelix of apoL1 [12]. Thus, apoL1 is the trypanosome lytic factor of normal human serum, and SRA confers resistance to lysis by interaction with apoL1 in the lysosome. Human susceptibility to trypanosomal infection is also known, since two genetic epidemiological studies conducted in Africa established that four single DNA polymorphisms located on genes coding for cytokines were correlated with a variable risk for development of the disease [11].

Due to trypanolytic activity of human plasma *T. evansi* has never been considered capable of infecting humans [13]. A few serological surveys were conducted in India, China, Somalia, and 2.5 to 4% of exposed population was positive using *T. evansi* or *T. lewisi* antigens [14]. A total of ten atypical cases of human trypanosomosis have so far been reported form Indian subcontinent. Out of these, nine cases were from India and one from Sri Lanka (Table 1). Three cases of human *T. evansi* have been reported from the Indian subcontinent (one from Sri Lanka and two from India) during the last decade. Apart from these three cases, at least four more atypical human cases of trypanosomosis caused by rat trypanosome, *T. lewisi* have been reported. Two casualties due to non-tsetse transmitted trypanosomosis (NTTT) were also reported from India [13, 14]. High prevalence ofthese two animal trypanosomes in India is now a matter of concern for public health specialists.

In summer 1999, a case of trypanosomosis was reported in patient in Colombo with the symptoms of headache and numerous trypanosomes in his blood were observed. Episodes of hyperthermia in the patient coincided with elevated number of trypanosomes in blood. The patient (a herdsman) had frequent contacts with cattle, which were suspected to be *T. evansi* infected. In February 2003, one Sri Lankan epidemiologist reported the patient extremely weak after undergoing many phases of exacerbation and effervescence of the disease, but was considered to be cured. Without knowing the treatment prescribed, the assumption was that this was a case of self-healing [11].

Twenty [15] atypical human cases of trypanosomiasis caused by animal trypanosomes are reported: 9 to *T. lewisi*, 5 to *T. evansi* and 4 of them are due to *T. brucei*, one to *T. vivax*, one to *T. congolense* and *T. brucei* species (Table 1). All cases due to *T. lewisi* were observed in Asia. Out of 20 cases, 6 are infants and 9 are from India. Two more cases have very recently been detected in Puducherry (unpublished). Particularly in the State of Maharashtra the concern is more serious because one case of *T. evansi* and two cases of *T. lewisi* have been reported in a span of 3 years. The environmental conditions in India are conducive to the spread of the parasite from animals to human beings [16].

The 1st atypical case was a 40 year old female suffering from headache and fever in West Bengal in 1903. Blood examination revealed *Trypanosoma* spp. The patient died two days after admission. The only *Trypanosoma* spp. which has been isolated from this area was *T. evansi* (Figure 1). This parasite is found in 8-10% of cattle and buffaloes in this area with

seasonal variation reaching a peak of 30% in monsoon [11]. Considering all the facts in absence of proper identification, it was presumed that the *Trypanosoma* spp. which was observed in the patient was *T. evansi*. Antibody levels in blood of general population using a highly specific card agglutination test for trypanosomiasis that uses Ro Tat 1.2 - a predominant variable antigen type of *T. evansi* [17] varied from 0% to 70% [15, 18].

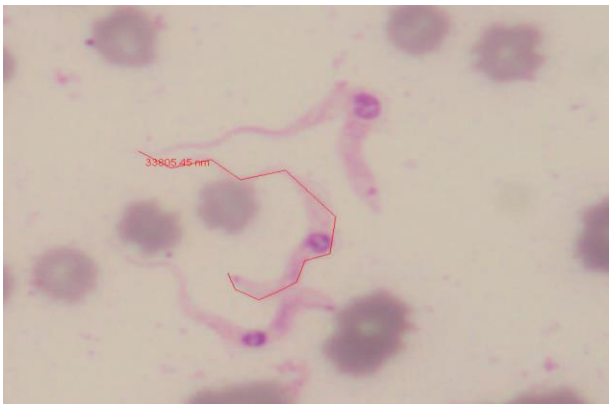


**Figure 1:** *Trypanosoma evansi* in blood smear with micrometry.

The first atypical human case of trypanosomosis in India, caused by *T. evansi*, was reported in September 2004 from a male herdsman of 45 years, staying in village Shivani block Sindewahi in Chandrapur district of Maharashtra, about 140 km. from Nagpur. The village has a population of about 3000 and is very close to the Tadoba Reserve forest. He had episodes of fever associated with sensory disturbances with violent behavior. Blood smear examination revealed presence of approximately $10^6$ trypanosomes/mL [16]. On the basis of parasitologic, immunologic, molecular diagnostic tests (PCR i.e. polymerase chain reaction) and genetic characterization, the parasite was identified as *T. evansi* [19]. Treatment with suramin (Virbac) intravenously @ 20 mg/kg weekly [16] led to complete cure after 6 months of initial infection. A series of investigations followed to ascertain the factors responsible for the occurrence of this unique case of *T. evansi*. Factors related to the infected person and the parasite isolate were investigated in great depth. The explanation for this unusual infection was related to the patient, whose serum was found to have no trypanolytic activity due to absence of APOL1, which was linked to frameshift mutation in both APOL1 alleles [20]. The amplification of the complete APOL1 was done, which revealed two different mutations, one allele, resulting in the absence of two bases, causing a frame shift mutation from residue 142 leading to a stop codon at position 149. For the other allele, the absence of a single base resulted in a frame shift mutation from residue 266 causing a premature stop codon at position 268. Both these mutations could be predicted to affect the pore forming functions [21]. A serological screening of 1806 inhabitants of the same village revealed 410 (22.7%) seropositivity by card agglutination test. However, it was also noticed that out of 60 persons who were positive at a high serum dilution, none was positive parasitologically, indicating frequent exposure of this population to animal trypanosomes through vector bite [21, 22].

The first report of atypical *T. lewisi* was from adult couple hailing from a rat-infested rural area from Raipur, Madhya Pradesh in 1974. Patients were suffering from fever and malaise and were found to have heavy *T. lewisi* parasitaemia [23]. Moreover again in September 2006, a recent case was a man aged 57 years, residing in a small village in district Pune (Maharashtra). He also depicted chronic intermittent fever, anemia, firm hepatosplenomegaly and edema on feet [24]. The investigations in March 2007 revealed that it was a case of *T. lewisi*. The primary epidemiological investigations showed no other cases in the village. The investigations pointed to the probability of transmission through rat fleas. Out of 8 rats trapped from the vicinity of the house, two were found positive for the same parasite by PCR [24]. Co-habitation of humans and rats in human dwellings both in urban and rural settings and human exposure to infected fleas might be responsible for host switching of *T. lewisi* from their natural rodent hosts to humans as suggested by Silva et al. [25]. The preliminary investigation before treatment reveled Hemoglobin (Hb) 8.7 g., white blood cell (WBC) 3,000, platelets 135,000, Serum creatinine 0.7, serum bilirubin 0.5, SGPT 11, alkaline phosphtase 273, apolipoprotein A154.06 mg/dl. Magnetic resonance imaging (MRI) revealed signs of cortical atrophy, ultrasonography showed splenomegaly [1]. After 1$^{st}$ dose of drug; Hemoglobin 7.7 g, white blood cell count 2800, platelets 47,000, serum creatinine 0.8, serum bilirubin 0.8, SGPT 96, alkaline phoshphatase 78, urine albumin positive. Bone marrow suppression was also observed resulting in moderate anemia and thrombocytopenia [1]. After 2$^{nd}$ dose of the drug the haematobiochemical levels were Hb 9.3 g, WBC 4600, platelets 184,000, serum bilirubin 0.6, SGPT 32, alkaline phoshphatase 86, serum creratinine -0.9, serum protein 7.8, serum albumin 3.1 [1]. During treatment the patient expired after second dose of

Suramin in 21 June 2007. After Postmortem parasites were seen in the pericardial and ascetic fluid but the cerebrospinal fluid (CSF) did not show trypanosome. The genetic study for mutation in the APOL 1 gene revealed that the four DNA fragments from the patient did not have any mutation in the amplified exonic fragments [1].

On 1 September 2006 a one and a half month old girl born of non-consanguineous marriage presented with fever since 5 days from Andheri, Mumbai. She was febrile and had hepatosplenomegaly. Peripheral smear showed presence of trypanosomes which were suggestive of the *T. lewisi* species in view of large size of kinetoblast, pointed posterior of cell and lack of undulating membrane. Haematobiochemical parameters were also altered [26, 27].

In 2014 at Nagpur, Maharashtra an adult male, a farmer and who kept cattle and sheep presented with history of febrile episodes on and off since 12 months. On examination he had anemia, firm splenomegaly and edema on feet. He received the second dose of intravenous Suramin (for *T. lewisi*) in the intensive care unit (ICU) under strict medical supervision. The patient was symptomatically better following this therapy and was thus discharged with regular follow-up advice [15].

## References

[1] Doke PP, Kar A. A fatal case of *Trypanosoma lewesi* in Maharashtra, India. Ann of Trop Med Public Health 2011; 4(2): 91-95.

[2] Johnson PD. A case of infection by *Trypanosoma lewisi* in a child. Trans R Soc Trop Med Hyg 1933; 26: 4678.

[3] Sarataphan N, Vongpakorn M, Nuansrichay B, Autarkool N, Keowkarnkah T, Rodtian P. Diagnosis of a *Trypanosoma lewisi* like (Herpetosoma) infection in a sick infant from Thailand . J Med Microbiol 2007; 56: 111821.

[4] Howie S, Guy M, Fleming L, Bailey W, Noyes H, Faye JA. A Gambian infant with fever and an unexpected blood film. PLoS Med 2006; 3: 150812.

[5] Woo PTK. Salvarian trypanosomes producing disease in livestock outside of sub-saharan Africa. In *Parasitic Protozoa.* Vol. 1, Academic Press, New York, 1977; 269-296.

[6] Bal MS, Singla LD**,** Kumar H, Ashuma, Gupta K and Juyal PD. Pathological studies on experimental *Trypanosoma evansi* infection in swiss albino mice. J Parasit Dis 2012; 36: 260-264.

[7] Reid SA. *Trypanosoma evansi* control and containment in Australasia. Trends in Parasit 2002; 18: 219-224.

[8] Touratier L, Thevenon S, Desquesnes, M. Efficiency of a trypanocidal therapy on a Trypanosoma evansi infected herd of dromedary camels in France: Evaluation along a 30-36 month follow-up under monthy checking. *XX National Congress of Veterinary Parasitology* held from 18-20 February, 2010 at CCS HAU, Hisar.

[9] Pays E, Vanhollebeke B. Mutual self defence: The trypanolytic factor story. Microbes Inf 2008; 10: 9859.

[10] Pays E, Vanhollebeke B, Vanhamme L, PaturiauxHanocq F, Nolan DP, PérezMorga D. The trypanolytic factor of human serum. Nat Rev Microbiol 2006; 4: 47786.

[11] Truc P, Buscher P, Cuny G, Gonzatti MI, Jannin J, Josh P, Juyal PD, Lun ZR, Mattioli R, Pays E, Simarro PP, Teixeira MMG, Touratier L, Vincendeau P, Desquesnes M. Atypical Human Infections by Animal Trypanosomes. PLOS Neg Trop Dis 2013; 7(9): e2256

[12] Gibson WC. The SRA gene: The key to understanding the nature of *Trypanosoma brucei rhodesiense*. Parasitology 2005; 131: 14350

[13] Juyal PD, Singla LD, Saxena HM. *In vivo* activity of human serum against *T. evansi* infection in Swiss albino mice. J Parasitic Dis 1998; 22: 67-68.

[14] Truc P, Touratier. Tuding atypical human trypanosomosis: towards an international network initiative. *Annual Report of O.I.E., Bordeaux, France, Annexure X*. 2010.

[15] Warpe BM, More SV. A rare Indian case of human trypanosomiasis caused by *Trypanosoma lewisi*-like parasites. J Biosci Tech 2014; 5(4): 564-567

[16] Joshi PP, Shegokar VR, Powar RM, Herder S, Katti R, Salkar HR, Dani V, Bhargava A, Jannin J, True P. Human trypanosomiasis caused by *Trypanosoma evansi* in India: the first case report. Am J Trop Med Hyg 2005; 73: 491-495.

[17] Sarkar A, Dey SK, Das S. Heterodistribution of *Trypanosoma evansi* Ro Tat 1.2 antibody levels in general population of West Bengal, India. 13th International Congress on Infectious Diseases, Kuala Lumpur. 2008. http://dasresearch.com/ recent papers.htm

[18] Das L, Touratier. Chagas antibody and *Trypanosoma evansi* Ro Tat 1.2 antibody levels in children of West Bengal, India - a preliminary study. 5th World Congress of the World Society for Paediatric Infectious Diseases, Bangkok, Thailand: 2007. http://dasresearch.com/publication.htm

[19] True P, Gibson W, Herder S. Genetic characterization of *Trypanosoma evansi* isolated from a human patient in India. Inf Gen Evol 2007; 7: 305-307.

[20] Vanhollebeke B, True P, Poelvoorde P, Pays A, Joshi PP, Katti R, Jannin JG, Pays E. Human *Trypanosoma evansi* infection linked to a lack of Apolipoprotein L-I. *N.* Engl J Med 2006; 355: 2752-2756.

[21] Pai-Dhungat JV, Parikh F. Trypanosomiasis in India. J asso phy India 2015; 63.

[22] Shegokar VR, Powar RM, Joshi PP, Bhargava A, Dani VS, Katti R, Zare VR, Khanande VD, Jannin J, True P. Short Report: Human trypanosomiasis caused by *Trypanosoma evansi* in a village in India: Preliminary serologic survey of the local population. Am J Trop Med Hyg 2006; 75: 869-870.

[23] Shrivastava KK, Shrivastava GP. Two cases of *Trypanosoma* (Herpetosoma) species infection of man in India. Trans R Soc Trop Med Hyg 1974; 68: 3-4.

[24] Banerjee PS, Basavaraj A, Kaur R, Rana UVS, Tewari AK, Baidya S, Rao JR, Raina OK. Fatal case *of Trypanosoma lewisi* in a human patient in India. 40h Asia-Pacific Academic Consortium for Public Health Conference, Vietnam, 2008; 4-6.

[25] Silva FM, Marcili A, Ortiz PA, Epiphanio S, Campaner M, Catao-Dias JL, Shaw JJ, Camargo EP, Teixeira MMG. Phylogenetic, morphological and behavioural analyses support host switching of *Trypanosoma* (Herpetosoma) *lewisi* from domestic rats to primates. Inf Gen Evol 2010; 10: 522-529.

[26] Shah I, Uma S. Ali US, Andankar P, Joshi RR. Trypanosomiasis in an infant from India. J Vector Borne Dis 2011; 48: 122–123.

[27] Shah MAA, Rehman K, Rehman F, He N.Present status of camel Trypnosomiasis in Pakistan, a review of literature. Sci. Lett. 2013; 1(1): 30-33.

[28] Kaur R, Gupta VK, Dhariwal AC, Jam DC, Shiv L. A rare case of trypanosomiasis in a two month oldinfantinMumbai, India. J Commun Dis 2007; 39: 71-74.