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Chagas Disease

AUTHORS DETAIL

Syed Muhammad Adnan Aslam[1], Muhammad Adnan Sabir Mughal[2], Muhammad Kasib Khan[2*], Khushbo Prince[3], Javeria Rashid[1], Ali Raza[4], Muhammad Hamza Azam[2] and Muhammad Usman[2]

[1]Faculty of Veterinary Science, University of Agriculture, Faisalabad
[2] Department of Parasitology, University of Agriculture, Faisalabad
[3] Department of Clinical Medicine and Surgery, University of Agriculture, Faisalabad
[4]Faculty of Veterinary Sciences, Bahauddin Zakariya University, Multan
*Corresponding author: mkkhan@uaf.edu.pk

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INTRODUCTION

Chagas disease is caused by the protozoan parasite *Trypanosoma* (*T.*) *cruzi*, also known as American trypanosomiasis. The disease was discovered in rural Latin America in the 20th century (1909) and currently affects about 6 million people worldwide. It is transmitted to the final host with the help of a Triatomine bug. The bug defecates during the blood meal and transmit *T. cruzi* to the final host through stercorarian route. Transplantation or congenital blood transfusion can transmit *T. cruzi*. These bugs usually live in crevices on the roofs of houses which are normally active at night and hide during daytime. This parasitic and chronic infection is the cause of cardiac or digestive complications that leads to patient death (Monteiro et al. 2022). This disease is called a silent disease because the symptoms of this disease in affected people may not be shown too early. The case detection rate for this disease is estimated to be 10%, creating a barrier to treatment and transmission. Every year around 12,000 people die due to complications from Chagas disease, with only 1 in 10 persons being diagnosed. Of these affected people, only a few receive treatment. A decrease in cases has been seen from 1980 to 2010 when the cases reduced from 17 million to less than 6 million. This was made happen by interrupting the blood transfusion transmission (LE et al. 2020). Animals are also seen to serve as carriers including rabbits, cats, and rodents. Dogs and cats are recognized as reservoirs of parasites (Gürtler et al. 2007).

The Chagas disease affect both humans and animals and has a large number of cases every year. Considering the significance of protozoa, this chapter briefly describes the parasite morphology, prevalence, life cycle, treatment, and various control strategies to reduce the infection rate.

Morphology

T. cruzi consists of a single tubular mitochondrion and has features like mammalian cells i.e., cristae and the presence of DNA (WHO 2002). In the mitochondria, the Kinetoplast consists of a DNA network comprising 22-25% of the total parasite DNA called kinetoplast DNA (Macedo et al 2010). *T. cruzi* whose developmental stages lack kinetoplast form can't perform a normal cycle. The shape and size of kinetoplasts fluctuate during different stages of development. Metabolic and structural changes in parasitic life cycle occurs due to multiple biological changes that make infection visible (Vickerman 1985).

The vector of disease is a triatomine bug belonging to the family Reduviidae, subfamily Triatominae and order Hemiptera (Corrêa et al. 1998). The protozoan parasite consists of three evolutive forms i.e., amastigotes, epimastigotes and trypomastigotes that can be identified with optic microscopy, by keeping in view the kinetoplast position in comparison to the nucleus and with the help of flagellum visibility (Hoare 1972).

T. cruzi contains an intracellular form that is the amastigote form seen in the tissues of the vertebral host. There is a lack of exterior flagellum and undulating membrane. Its measurement is 4.0 µm in diameter. The binary division takes place every 12 hours and trypomastigote is formed roughly 10-12 hours before rupturing of the cell. The amastigote stage forms and can infect newly formed cells in circulation (Ley et al. 1988).

The epimastigotes form is present in the opossum anal glands and the triatomine digestive tract. A kinetoplast and the flagellum are present before the nucleus, a poorly developed membrane is also present, measuring up to 40µm, and consisting of freely floating flagellum. In general, the nucleolus at the nucleus's center position is present (López-Velázquez et al. 2005). It shows movement and presents highly replicative activity. The binary division also seen, forming rosacea. The temperature of 37 ^{0}C severely affects the evolutive form, while the range of 20-28 ^{0}C shows a better development. (Kleisen et al. 1976; Pollard et al. 1990; Florencio-Martínez et al. 2010).

In trypomastigotes, the ability to replicate is lacking, but submembrane microtubules are present that perform many functions i.e., cell differentiation, motility and tissue

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migration and are considered extrinsic infectious forms. There are two kinds of trypomastigotes found in the cells of invertebrates and vertebrate hosts. Metamorphic trypomastigotes are found at the end of the intestine or may be present in Malpighian tubules. Morphologically, it is similar in appearance to narrow form of the blood trypomastigotes, up to 17μm in size. A shorter flagellum appears near the basket-shaped kinetoplast, and a narrower wavy membrane appears along it. Blood and other body fluids may have trypomastigotes in the blood. The size of the wave film ranges from 12 to 20μm (Logan and Menko 2019).

Prevalence

Initially, Chagas disease was observed in Latin America in the early 16th century, affecting European people (Miles 2004). In 1950, the first vector-borne Chagas disease was reported in the United States. Immigration also contributes to the disease increase from endemic to non-native countries (Develoux et al. 2010).

From 1994 to 1998, donor screening was conducted in Los Angeles and Miami to find donors who had been born in or had previously travelled to Chagas disease-endemic countries (Leiby et al. 2002). Of these, 7.3% of the donors from Los Angeles and 14.3% from Miami were identified as high-risk donors. With radioimmunoprecipitation assay (RIPA) validation and enzyme immunoassay (EIA) screening, *T. cruzi* was detected in 7,500 donors in Los Angeles and 9,000 donors in Miami. The Los Angeles seroprevalence rate increased each year dramatically during the study period. On average, 25,000 to 30,000 donors were screened for seropositivity. Seroprevalence was highest in places with large populations of immigrants from endemic countries. In 2009, it was estimated that up to 300,000 US immigrants had chronic *T. cruzi* infection, almost 30,000 to 45,000 cases of Chagas cardiomyopathy and up to 300 congenital infections annually based on immigration and seroprevalence data in endemic countries (Bern et al. 2011).

Europe has reported isolated cases of Chagas disease since 1980s (Pehrson et al. 1981). According to the International Organization for Migration, the migration to Europe especially southern Europe has increased since 2000. According to census data from countries where Chagas is endemic, there were an estimated 4,83,074 legal immigrants from Latin America residing in European countries in 2005. 14,010 (2.9%) of them were considered contaminated and 2,803 acquired medical attention (Schmunis and Yadon 2010).

Life Cycle

Life cycle is completed in two different hosts i.e., vertebrate host include human and invertebrate host include reduviid or bed bug (*Triatoma infestans*). The infective metacyclic trypomastigote stage is injected in to vertebrate host through faeces of vector during the act of biting. The faecal material is being rubbed on the wound created during blood meal. Metacyclic trypomastigote is invasive in nature and penetrate various cells at the site of wound and transformed in to the amastigote stage. This stage start multiplying by binary fission inside the cells of infected tissues. Afterward, this stage gets converted to trypomastigote stage which is then released from the infected tissues after bursting the cell and enter in the blood stream. Trypomastigote can be converted back to amastigote stage and infect other tissues in the vertebrate host. When vector takes a 2nd blood meal from same host, it ingested the trypomastigote stage with blood. Trypomastigote stage transformed to epimastigote stage in the midgut of vector followed by the multiplication of epimastigote through binary fission. It is then transformed to trypomastigote stage in the hind gut of vector which ultimately injected again in the vertebrate host. Fig. 1 illustrate various life cycle stages of *T. cruzi* in vertebrate and invertebrate hosts (Rassi and Marin-Neto 2010).

Clinical Signs

Acute Infection

The parasite needs 1-2 weeks for incubation. The intense phase lasts almost 12 weeks. Patients with this parasite usually are asymptomatic. Only nonspecific symptoms are visible, like fever, headache, diarrhea, and vomiting. They do not need any medical care (Prata 2001). Only 1% of people show severe conditions like myocarditis and pericardial effusion. Acute disease has a danger of mortality rate of upto 0.2–0.5%. Under a microscope, trypomastigotes appear like a smear of a bluffy coat. In some patients, blister forms at the injection site which is usually referred as chagoma. Lesions may also be formed. The occurrence of disease is more in older people than the children older than two years of age. Orally transmitted *T. cruzi* infection causes more mortality and morbidity (Carod-Artal 2007). During an outbreak in Venezuela almost 75% of infected people were symptomatic, 59% individuals were seen having ECG abnormalities, among them 20% were treated, and there were 1% death rate (Alarcón de Noya et al. 2010).

Congenital Infection

Most contaminated neonates are asymptomatic or show minimal symptoms, while a small percentage develop a severe life-threatening illness (Bern et al. 2009). The clinical signs of symptomatic congenital Chagas disease include hepatosplenomegaly, anemia and thrombocytopenia (Bittencourt et al. 1981). Meningoencephalitis, gastrointestinal mega syndromes, anasarca, pneumonitis, and/or respiratory transportation are among the severe neonatal complications that may occur. According to published data, newborns with infections typically die between 5% to 20% more than infants without infections (Torrico et al. 2004).

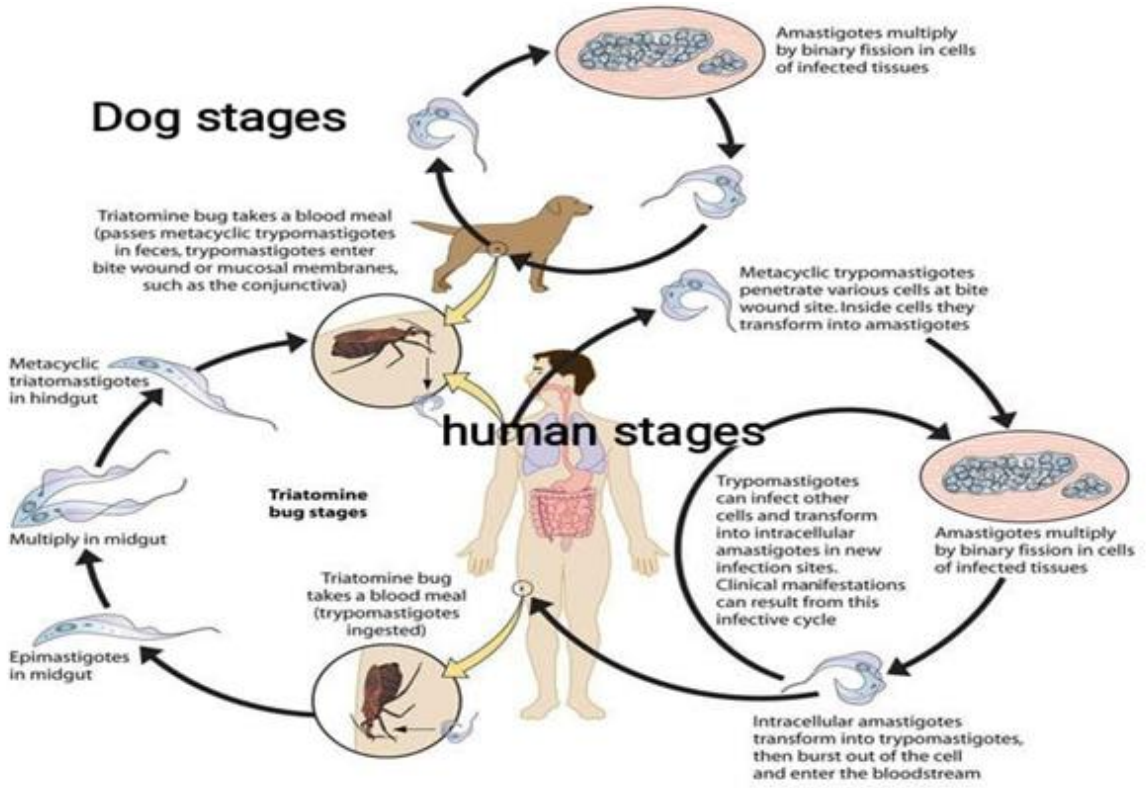

Fig. 1: Life cycle stages of *T. cruzi* in vertebrate and invertebrate hosts

Chronic Infection

After 8-12 weeks of infection, when parasitemia levels are no longer visible under a microscope, the person enters the frightful period of *T. cruzi* contamination in the nonappearance of successful etiological treatment. People with terrible *T. cruzi* infection can indirectly transmit the parasite to other individuals through blood components, organ contribution and congenital transmission despite the lack of minute parasites in the peripheral blood (WHO 2002).

Diagnosis

Depending on the stage of the disease and the status of the patient suitable diagnostic test for *T. cruzi* infection can be performed.

Diagnosis of Acute Infection

Motile trypomastigotes can be found during the acute phase under a microscope using the latest anticoagulated blood preparations or buffy coat. Parasites can also be observed under a microscope using Giemsa stain or other dyes on blood smears. While relatively sensitive during the acute phase, hemoculture in one of the standard parasite mediums taking two to four weeks to show reproduction. Within 90 days of infection, even without therapy, the parasitemia level declines and becomes microscopically undetectable during the chronic phase. PCR can be performed to detect the infection in patients who got the infection unintentionally or received an infected organ (Wegner and Rohwedder 1972).

Diagnosis of Congenital Infection

Similar diagnostic procedures are used for congenital Chagas' disease, which manifests as an acute *T. cruzi* infection in infancy. Fresh blood testing is less sensitive than the concentration methods. The procedure most frequently used in medical facilities in Latin America is the microhematocrit technique. With the help of light microscopy buffy coat layer is surveyed (Feilij et al. 1983). After delivery, parasitemia levels rise which peak up to 30 days or more. Repeated sampling within the first few months after delivery increases the sensitivity (Mora et al. 2005). Although the process is uncommon, but the molecular methods can identify congenital contaminants advance in life (Duffy et al. 2009). In developed nations like Latin America, PCR is the selected procedure for the timely identification of congenital disease. After nine months of age, when the transmitted maternal antibody has vanished, and the congenital infection has transitioned into the chronic phase, conventional IgG serology is advised for infants not identified at birth (Carlier and Truyens 2010).

Diagnosis of Chronic infection

Two serological examinations built on several procedures, such as immunoblotting, IFA and ELISA, are employed to boost the validity of the result because no single analysis has sufficient sensitivity and distinction to be relied upon lonely (WHO 2002).

Inevitably, some people subjected to two different tests whose serological results are inconsistent may require additional testing to determine their infection status. Because findings from less sensitive tests may yield negative results, specimens with the positive outcome but low antibody titers are probably disposed of the discrepancy. (Umezawa et al. 1999; Sosa-Estani et al. 2008). Trypomastigote-eliminated antigen immunoblot (TESA-blot) is another technique used to diagnose the chronic infection, but it does not have better susceptibility and may not be able to accurately identify the infection (Leiby et al. 2000). FDA has approved several ELISA kits for diagnostic use. Instead of relying on internal outcomes for which there are no conducting facts, it is preferable to utilize an assay with validation data (Bern et al. 2008).

Utility of PCR for Diagnosis

Accurate method for diagnosing acute stage and early congenital Chagas' illness, as well as checking for critical *T. cruzi* contamination in recipients of spoiled organs or after unintentional exhibition, is using PCR method (Chin-Hong et al. 2011). PCR assays typically produce positive results before the appearance of circulating trypomastigotes on peripheral blood smears (Schijman et al. 2000). The immunosuppressed host with *T. cruzi* contamination can be tested for reactivation using quantitative PCR techniques. An untimely and tactful predictor of reactivation in these patients is quantitative PCR testing, which shows growing parasite levels over time. Conventional PCR results in these patients do not verify reactivation (Diez et al. 2007). PCR is utilized in long-term *T. cruzi* contamination as an investigation apparatus, but typically it is not an adequate diagnostic trial. Even though a percentage of patients will have positive PCR results, the sensitivity varies greatly depending on the aspect of the residence being examined and PCR primers and techniques. For these reasons, negative PCR findings do not prove the absence of infection. (Basquiera et al. 2003).

Treatment

Only benznidazole and nifurtimox have been shown to effectively treat Chagas disease. Other medications besides these can be employed, but only by the inquiry procedure. A nitrofuran called nifurtimox disrupts the metabolism of carbohydrates in *T. cruzi* by preventing the formation of pyruvic acid. Between 30 % to 70% of patients experience side symptoms relating to the digestive system. Anorexia is included, which causes loss of weight, motion sickness, nausea and disconcertment in the abdomen. The symptoms of neurological poisoning, such as irritation, sleeplessness, confusion, and, less frequently, tremors, are also very typical. Polyneuropathy, peripheral neuritis and paresthesia are uncommon but have more severe adverse effects. The peripheral neuropathy, dependent on dose, develops late in therapy. Infants receive higher doses than older children, while children generally have better medication tolerance. A nitroimidazole derivative called benzmidazole is thought to be more trypanocidal than nifurtimox. The most common dermatological adverse effects are photosensitization-related rashes, which rarely proceed to exfoliative dermatitis. Dermatitis that is severe, exfoliative, or connected to a fever and lymphadenopathy should cause the medicine to be stopped right away. Peripheral neuropathy is dependent on dose, typically develops late in therapy and is a sign that treatment should be stopped immediately. This is reversible, but it may take months to determine. Beginning nine to ten days following the start of the analysis, patients should be checked for dermatological side effects (de Andrade et al. 1996).

Treatment of Acute and Congenital infection

Both medications lessen the simplicity of the signs, shorten the distance course, and shorten the period of apparent parasitemia in critical and early congenital Chagas disease. Nifurtimox was used in the initial anti-trypanosomal medication trials in the 1960s and 1970s on individuals with acute Chagas disease. 81% of patients who received acute phase treatment had serological cure verified at the 12-month follow-up (Bern et al. 2011).

Treatment of Chronic *T. cruzi* Infection

Antiparasitic drugs were thought to be only helpful during the acute phase, which includes early congenital infection. In contrast, two placebo-controlled studies were conducted in the 1990s on children with persistent *T. cruzi* infection and benzmidazole showed a cure rate of 60% (Gascón et al.2007).

Prevention

To prevent from chagas disease following precautionary measures must be taken:

- Using of insect powder and spray gun
- Have proper house cleanliness.
- Must follow different preventive measures such as transportation of food, consumption, and storage.
- Conduct seminars to provide awareness about this disease and how can we prevent it.
- Testing of organ, tissue or cell donors and receivers
- Do proper diagnosis and treatment of people with disease. specially women and children.

- Screening of infected mothers and newborn (Abad-Franch et al. 2010).

Conclusion

Chagas disease is caused by the protozoan parasite *T. cruzi*. Emigration of people from endemic to non-endemic region played a vital role in disease spread, which is heavily dependent on globalization. Lack of proper treatment and screening of infected people are significant causes of the spread of Chagas disease via non-vector routes of mother-to-child transmission and affected blood transmission. Despite various financial and political constraints, Chagas disease has been controlled through the invention of different medical and preventive techniques, social improvements, and transmission control. Comprehensive efforts are needed to engage immigrants and train healthcare providers to prevent the spread of disease.

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