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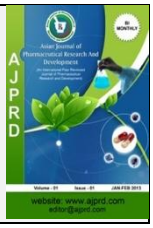

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Review Article

Clinical Signs and Pathogenesis of Trypanosomal Infection in Human and Animals

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A B S T R A C T

Trypanosomiasis is a chronic disease which affects both human and animals with high morbidity rate within months after exposure, particularly when poor nutrition or other factors contribute to debilitation. The disease has been a major threat to Human and public health concern and also has contributed negatively to food security in Nigeria. Trypanosomes are haemoflagellated parasites that suppress the host immune system through antigenic variation causing serious illness in man and direct losses in meat production and milk yield in animals leading to severe pathogenesis that result to death . The clinical signs of trypanosomisis have been reported as unnoticed, chronic and acute which can easily lead to death, while the pathogenesis are severe and diverse. A vast majority of human and ruminant animal such as cattle, sheep and goats can be infected without clinical signs. In this paper, we documented some of the major pathogenesis of trypanosomiasis that are leading cause of death and they includes Aneamia, Immunodepression, Immunosuppression, Myocarditis, oedema, loss of conditions, coma as well as infection of various organs and tissues. The paper recommend that further work on pathogenic mechanisms of trypanosomiasis need to be carried out so as to notice the exact clinical sign of the disease which will help towards controlling the disease.

Keywords: Pathogenesis, Trypanosomes, Anemia, Oedema, Myocarditis.

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INTRODUCTION

Trypanosomiasis is a chronic disease which affects some 36 developing African countries with about 300,000 new cases that are reported annually[1]. The disease affects both human and animals with high morbidity rate of about 50-100% within months after exposure, particularly when poor nutrition or other factors contribute to debilitation[2]. Trypanosomiasis has been the major Threat to Human and public health concern and also has contributed negatively to food security in Nigeria[2]. This is due to the suppression of the host immune system by the Trypanosomes, resulting to a serious illness in man and direct losses in meat production and milk yield in animals leading to severe pathogenesis and other unnoticed clinical signs such as anemia, loss of production, pyrexia, lacrimation, pallor of the mucus membrane, weight loss, infertility and abortion, coma and finally leading to death during the acute phase of the disease[3]. Trypanosomes are haemoflagellated parasites belonging to the genus *Trypanosoma*, the Family *Trypanosomatidae* and the order *Kinetoplastida*[4]. These parasites are further grouped in to subgenus Duttonella (the vivax group such as *Trypanosomavivax*, which infects a large number of wild and domestic animals), subgenus Nannomonas (the congolense group, such as *T. congolense*, *T. simiae* and *T. godfreyi*) and the subgenus Trypanozoan (the Brucei group such as *T. brucei brucei*, *T. brucei gambiense*, *T. bruceirhodesiense*, *T. evansi, and T. equiperdum*)[5]. Amongst these parasites, the sub-species *T. b. brucei* is reported to be the most virulent trypanosome, this is due to

the presence of a dense protein layer consisting of a single protein called the variable surface glycoprotein (VSG). This acts as a major immunogen and elicits the formation of specific antibodies, thus enabling the parasites to evade the consequences of the host immune reactions by switching the VSG, a phenomenon known as antigenic variation causing severe, and fatal disease in a specific host[6]. Trypanosomes are transmitted by obligatory blood suckers tsetse flies that feed on infected animals and undergo cycles of development[7]. After infection through the bite of a tsetse fly, the parasite proliferates rapidly by binary fission and invades Lymph and blood vessels and then progressively disseminate to the bone marrow and tissue resulting to a various clinical sings that are unnoticed which can easily lead to death[8]. As such, more information on the pathogenesis and clinical signs of this disease need to be investigated so as to notice the exact clinical sign of the disease which will help towards controlling the disease.

RESULTS AND DISCUSSION

Like all other infectious diseases, the clinical sign of Trypanosomiasis starts with an increase in body temperature, a condition known as hyperthermia[5]. This occurs as a result of the contact between the trypanosomes and the defense system of the host[4]. However, human and some ruminant animal such as cattle, sheep and goats can be infected without clinical sign[9]. Most clinical cases are chronic, but acute disease, which may be fatal within weeks, can also be seen. The first sign may be a localized swelling (chancre) at the site of the fly bite, but this usually remains unnoticed[10]. The primary clinical signs are an intermittent fever, pale mucous membranes, lethargy, lymphadenopathy, weight loss and hypoglycemia in the acute stage[11]. However, loss of condition and decreases in milk yield in some animals has also been reported[9]. Neurological signs, dependent edema, cardiac lesions, diarrhea, corneal opacity, abortions, premature births, perinatal losses, orchitis, epididymitis as well as reduced in semen quality were also documented[12]. Sudden deaths have been reported in untreated animals with chronic clinical sin[13]. The Mechanism of the clinical sign start, when the tsetse fly injects infective metacyclic trypanosomes in to the skin of the host, in which a local inflammation and a swelling known as chancre develop[5]. The metatrypanosomes divide and multiply in the chancre giving rise to the typical blood forms which invade the lymphatic and lymph nodes, and then to blood stream[4]. Eventually, the parasites enter the blood circulation via lymph vessels and can survive in the blood circulation throughout the infection and remain continually exposed to the host's immune system[9]. *T. brucei* has the ability to penetrate the walls of capillaries, invade interstitial tissues, but always remain extracellular. *T. congolense* is an extracellular, intravascular blood parasite that is unable to leave the circulation. It has a tendency to bind to walls of capillaries and small vessels[9]. The surface protein of trypanosomes provoke the host in making specific antibodies against these proteins, and after a few days all the trypanosomes in the blood are destroyed by these antibodies and the body temperature drops, but few trypanosomes survive and multiply causing a new peak of parasitaemia and hyperthermia, until the organism of the host make a new specific antibodies against the new surface proteins[12]. This process continues for a long time, until the antigenic receptors of the trypanosomes is finally exhausted[14].

ANAEMIA

Trypanosomiasis possess different clinical signs and pathogenesis on the host body at varying degrees and severity resulting to a death. As such, Anaemia is one of the major pathogenesis of trypanosomiasis[4]. Most deaths reported due to trypanosomal infections occurred in association with anaemia, hence is regarded as the leading cause of death in trypanosomiasis[1]. Is the process by which the Haemoglobin in the blood is reduced or decreased, in which insufficient oxygen in the cell for their functioning and efficiency of their normal activities is reduced, resulting in the deterioration of health condition and death[5]. Anaemia tends to develops in trypanosomias is due to the rapid haemolysis of the red blood cells by invading trypanosome[1]. However, Many factors contributes to the development of trypanosomal anaemia[1,10,12].These includes: general destruction of infected red blood cells and their shortened survival life time, accelerated destruction of the red blood cells by the immune system, the suppression of the bone marrow response by cytokines, massive gastrointestinal hemorrhage and increased spleen Clarence of infected red blood cells leading to tiredness, breathlessness, fever and weakness, prostration, platelet aggregation, malnutrition, tumor necrosis, severe left ventricular failure, pulmonary oedema, heart attack and finally death[10]. Anaemia in Trypanosomiasisis is morphologically classified as macrocytic and normochromic which all occurs in three main phases: acute phase, chronic phase and recovery phase[19]. In the acute phase of trypanosomiasis, there is higher number of parasitemia, with higher number of trypanosomes in peripheral circulation[20]. This lead to the severe pancytopoenia and finally death[21]. However, the phagocytosis of the red cells by the white cells occurs, in which the red cells becomes coated with material from the lysed trypanosomes which tricks the phagocytes into mistaking them for foreign invaders and remove them[20]. As a result, the haemopoietic system then compensate for the loss of erythrocytes by increasing its activity[5]. In the chronic phase of trypanosomiasis, the trypanosomes produces other toxins which have a depressing effect on the haemopoitic system[20]. This makes the host immune sytem unable to produce red cells. However, this phase is characterized by low levels of parasitaemia with less trypanosomes in peripheral circulations[21] . The Recovery phase is the last phase of anaemia in trypanosomiasis and is characterized by the low and absence of parasitaemia[21]. At this stage, declined erythrocyte values begin to return towards pre-infection values and other pathological changes undergo resolution leading to self-recovery[20, 21]. To manage Aneamia, iron and folic acid supplements have been recommended, but in some condition, where the haematocript value is less than 20%, blood transfusion is

urgently recommended so as to prevent death[9,5]. The mechanism of anemia in Trypanosomiasis is complex and multifactorial in origin[10]. Which is greatly associated with the generation of free radicals and super oxides following lipid peroxidation[14]. Peroxidation causes erythrocytes to produce large quantities of lipid peroxidation byproducts. These oxidative products attack erythrocyte membrane polyunsaturated fatty acids and proteins directly leading to oxidative hemolysis and damage of their integrity[15]. Erythrocytes of infected host possess decreased antioxidant ability and are unable to withstand oxidative stress[9]. Lipid peroxidation of membranes is associated with a decrease in membranes fluidity and in the activities of membrane-bound enzyme[15,9] . Trypanosomes can alter erythrocyte membrane fluidity and a decrease in erythrocyte membrane-bound enzymes[9,12]. Immune Complexes Immunological mechanisms are major reasons for the removal of erythrocytes. Red cell surfaces may bind auto or poly reactive antibodies, or may passively absorb trypanosome molecules followed by binding of antitrypanosome antibodies with subsequent removal from the system[16,15] . There is an overwhelming proliferation of tissue macrophages through lymphokines, antigen-antibody complexes and C3b complement fragments[9,16]. Malnutrition Trypanosomiasis may cause a drop in feed intake hence there is energy deficit and loss of tissue associated with catabolism of body fat, protein, deficiencies of vitamin C, B and essential amino acids[9]. Inadequate energy supply to erythrocytes may alter the erythrocyte membrane surface therefore leading to weakening of the cell membrane, increased osmotic fragility and hemolysis[10]. Tumor Necrosis Factor and Nitric Oxide Development of anemia in inflammatory diseases is cytokine-mediated, especially tumor necrosis factor-α (TNF-α) produced by activated macrophages[15,16]. One of the ways that TNF-α influences erythrocyte levels is by regulating erythropoietin (EPO) production. IL-1 and TNF-α are responsible for the defect in EPO production by suppressing EPO gene expression[9]. It was reported that, Bone marrow cell population from *T. brucei* infected mice exhibited increased levels nitric oxide (NO) production in the bone marrow and coincided with suppressed T-cell proliferation[10,12,14]. Immunopathobiology Trypanosomes appear to activate, modulate and control many aspects of host innate and acquired immunity during infection[19]. The antigens released by trypanosomes elicit immunochemical reactions associated with the proliferation and activation of macrophages, complement activation, inflammation and autoimmune disease[9]. Major modifications of the immune system were observed in African Trypanosomiasis: lymphadenopathy, splenomegaly (up to thirty times the normal size) with destruction of lymphatic tissue architecture. These Immune reactions do not lead to protection but are involved in immunopathological disorders that may induce tissue alterations[18]. The major surface component (Variant surface glycoprotein, VSG) is associated with escape to immune reactions via the phenomenon of antigenic variation, resistance to complement lysis, cytokine network dysfunctions (in particular TNF-α) and autoantibody production[14,18].

Immunodepression and Immunosuppression

Trypanosomiasis is also associated with Immunodepression [4,5] . In this case, the immune system of the host becomes less efficient to fight infections resulting to the depression in the haemopoietic system. Immunodeprsssion usually occurs at the acute phase of trypanosomiasis, in which the ability of the immune system to respond and react to invaders is totally diminished[5]. Host effected with this condition usually develop a lower antibody titer after vaccination against other disease, and secondary infection also come up. However, Immunosuppression in Trypanosomiasis is attributed to polyclonal B cell activation as well as the generation of suppressor T cells and suppressor macrophages[9]. Polyclonal B-cell activation is a major immunosuppressive event in a variety of pathogens, as it is believed to divert the specific response against the parasite[22]. Phagocytosis of whole trypanosomes, membrane fractions or glycolipid fractions of the membranes could result in immune-supression[9]. The major component of trypanosomes that activates macrophages appears to be the GPI, the membrane anchor of the VSG[9]. Such macrophages are highly activated, producing prostaglandin E2, plasminogen activator, H2O2, O-2, IL -1, but have lower expression of mannose receptor, FcR and CR3[9].They also produce enhanced amounts of TNF-α, IL-6, IL-12, IL-10 and NO[23]. There appears to be a general deregulation of macrophages, eventually leading to their apoptosis[24]. Prostaglandin E2 produced by the suppressor macrophages contributes to further immunosuppression, possibly by reducing the production of IL-2[9,14]. T-lymphocyte unresponsiveness is thought to result from a depression of IL-2 and IL-2 receptor production, which are induced by suppressor macrophages[25].

Oedema

Trypanosomiasis can also lead to subcutaneous swellings caused by accumulation of tissue fluid known as Oedema[3]. This causes an increased in permeability of blood capillaries and leakage of blood plasma leading to swellings[4,5,6] .

Myocarditis

However, in the chronic form of trypanosiomiasis, an inflammation of the heart muscle known as Myocarditis do occurs. This result to a heart failure and finally lead to death[3]. However, this depends on a large degree on the effort of the heart muscle. Extensive Myocarditis is usually associated with infection caused by pathogenic West African *T. vivax*[5,2,4].

Organs and Tissues Infections

Various organs and tissues of the host are infected depending on the trypanosomes species involved[26]. Example, *T. vivax* is found in the lymph and in the chamber of eyes where it causes infection, *T. congolense* is mainly found in the blood and causes blood infection. *T. bruce*i is well known to invade the central nervous system in human sleeping sicknes while in some animals like horses, goats,

and dogs the nervous system is affected by *T. equiperdum*[6,4].

Lose of Conditions

In the chronic trypanosomiasis the host loses condition resulting to a wasting. During the acute stage, the appetite is variable being decreased during the fever peaks[5,4]. But in the chronic form, when the fever reaction are less pronounced, the appetite is usually normal[26] . However, There is consumption of the food reserves during the recurrent bouts of fever, but also severe as degenerative changes of the muscle cells and other issue cells as well as an increased breakdown of protein in muscles leading to atrophic degeneration[5,26].

Coma

However, Coma has also been reported as one of the most dangerous and feared complications of severe Trypanosomiasis[5]. Coma in trypanosomiasis occurs due to metabolic acidosis as a result of general tissue oxygen due to the combination of various interactions by the trypanosomes and the host. However, Mechanical blockage of the microvasculature by sequestered parasitized red blood cells have been reported in the brain cells in addition to cytokines activation leading to brain damage and other cellular pathology and finally death[4,9,26].

CONCLUSSION

Based on the results of several studies, it can be concluded that both human and animals are infected with trypanosomes but the clinical sings remain unnoticed[12,13]. However, this work will serve as a guide to researchers and scientists towards coming up with an intensive research on the mechanisms of pathogenesis in trypanosomiasis which will provide information on the treatment and control methods of the disease. In this paper, we documented some of the major clinical sings and pathogenesis of trypanosomiasis that are leading cause of death and they include Aneamia, Immunodepression, Myocarditis, oedema, loss of conditions, coma as well as infection of various organs and tissues. The paper recommend that further work on the mechanisms of trypanosomal pathogenesis need to be carried out so as to notice the exact clinical sign of the disease which will help towards controlling the disease.

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