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Review Article

How do Viruses Cause Pyrexia?

Raghavendra Rao MV[1]*, Jattavathu Madhavi[2], Dilip Mathai[2], Vijay Kumar Chennamchetty[2], Abrar Khan[3], Farooq Shaik[2], Tiara Calvo[3], Gil Apacible[3], Frank Michael Navarrete[3] and Abigail Apacible[3]

[1]Scientist Emeritus, Central research laboratory, India

[2]Professor of Medicine, Apollo Institute of Medical Sciences & Research, India

[3]Professor, American University School of Medicine Aruba, USA

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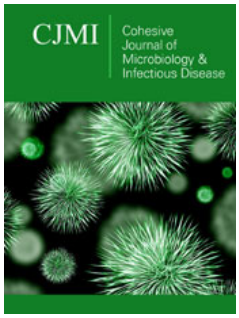

***Corresponding author:** Raghavendra Rao MV, Scientist Emeritus, Central research laboratory, India

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Abstract

Fever occurs typically when a virus or bacteria invades the body. Fever is certainly the most common systemic manifestation of the inflammatory response. The ultimate regulators of body temperature are the thermoregulatory centers in the hypothalamus They are subject to physical and chemical stimuli. Direct mechanical injury or the application of chemical substances to these centers results in fever. "Dengue is a mosquito-borne virus fever caused by a flavivirus. The disease was known as" Dandy Fever" or "Break bone fever". Dengue is called "Poor man's disease. Yellow fever is a mosquito borne acute febrile illness. It does not exist in India due to strict vigilance on vaccination and quarantine for travel from endemic areas. Marburg and Ebola viruses cause high fever, with bleeding into skin, and from the nose, gastrointestinal tract, and genitourinary tract; Thrombocytopenia and marked toxicity often leading to shock and death. Lassa virus is extremely virulent. The disease is characterized by high fever, mouth ulcers, skin rash with hemorrhages, pneumonia. *St. Louis Virus*, Coronavirus, Orthomyxovirus, Parainfluenza Virus and Measles Viruses also produce fever. Chikungunya, *O'nyong-nyong Viruses*, West Nile, Rift valley, Kyasanur forest disease fever, Omsk hemorrhagic fever, Colorado tick fever, Sandfly fever are also the viruses associated with pyrexia

Keywords: *St. Louis Virus*; Coronavirus; Orthomyxovirus; Parainfluenza Virus; Measles Viruses; Chikungunya; *O'nyong-nyong*; West Nile; Rift valley; Kyasanur forest disease fever; Omsk hemorrhagic fever; Colorado tick fever; Sandfly fever; Yellow fever; Dengue fever; Marburg, Ebola; Lassa virus

Introduction

Ebola virus is one of the most virulent pathogens known to infect human [1] the first recognized Ebola outbreak occurred in 1976, near the Ebola River in Zaire (now Democratic Republic of Congo, DRC) [2,3]. The current outbreak in West Africa has so far affected more people than all previous Ebola outbreaks combined [4]. The first human cases of Lassa fever (LF)were described in 1970 in the North-East Nigeria [5]. In1974, Lassa virus was isolated from its zoonotic reservoir, the multimammate rat [6,7]. Human to human transmission is also possible, although less frequent, and is most common in nosocomial context [8]. It is common in South America and Africa, but not in Asia [9]. The first identification of Marburg hemorrhagic fever (MHF) occurred during an 'outbreak' in Germany and Serbia (former Yugoslavia) in 1967 [10] All most all MHF cases have been reported from eastern Africa [11]. Ecological niche modelling has demonstrated that these areas are part of a large region with similar ecological conditions to those found in the previously known MARV endemic area [12] Crimean Congo Haemorrhagic Fever (CCHF) is severe forms of hemorrhagic fever endemic in Africa, Asia, Eastern Europe and the Middle East [13]. The CCHF virus is the most extensive among the tick-borne viruses that affect human health [14]. Dengue serology is complicated by 4 antigenically related serotypes [15].

Chronological record of significant events

It is not clear where the word "dengue" came from. Some people think that it comes from the Swahili phrase Ka-dinga pepo, caused by an evil spirit [16]. The disease was first identified in 1976, in Nzara, a town in South Sudan, a village near the Ebola River [17]. The disease was

identified in Nigeria in 1969. It is named after the town Lassa in which it was discovered [18]. Marburg virus was first described in 1967, in the German cities Marburg and Frankfort [19]. Infection of coronavirus was first known in the late 1920s when an acute respiratory infection of domesticated chickens emerged in North America [20]. Arthur Schalk and M.C. Hawn made the first definitive report in 1931 as a new respiratory infection of chickens in North Dakota [21]. In the late 1940s, two more animal coronaviruses, JHM that caused brain disease (murine encephalitis) and mouse hepatitis virus (MHV) were discovered [22]. Modern molecular biology places the emergence of measles as a human disease sometime after AD 500 [23] Recent studies suggest measles first appeared as early as the 4th century BC [24,25].

Research on the role of interleukins in fevers

IL-6 is a potent pyrogenic cytokine, trafficking to lymphoid organs during febrile events [26] IL-6 has been implicated in the progression of several virus infections [27] Direct evidence supporting the importance of IL-6 during viral infections has been gathered in experimental infections using IL-6-deficient mice [28,29]

Interleukins or Lymphokines are regulatory proteins secreted by monocytes or macrophages or T-lymphocytes. They are involved in signaling between cells of the immune system. Interleukins are a group of biologically active factors released by primed lymphocytes. Lymphokines can be secreted by both T and B lymphocytes, though T cells are assumed to be the main source. These are non-antibody proteins and polypeptides secreted by lymphocytes on contact with antigen. They act as intercell mediators in immune responses. There are many lymphokines which have a wide range biological activity. Many lymphokines show multiple biological activities and so the descriptive names can be misleading. A nomenclature interleukin is introduced followed by a number.Interleukin-1(IL-1).This was originally called as Lymphocyte Activating Factor (LAF) Initially ,it was observed to be secreted by monocytes and macrophages (hence known as monokine) but now it is known to be produced by all nucleated cells .The production of interleukin-1 is introduced by the antigens, lectins and lymphokines from T-cells such as macrophage activating factor.IL-1 stimulates B-cell proliferation, differentiation and synthesis of immunoglobulins. It activates T-cells and promote synthesis of lymphokines. It is endogenous pyrogen hence induces and stimulates an increase in acute phase serum proteins [30].

IL-1 consists of two proteins.IL-1 alpha, and IL-beta, both have exactly the same functions.IL-1 is produced by all antigen presenting cells, but activated macrophages and monocytes produce the same in relatively large amounts.IL-1 thus liberated from activated macrophages, binds to its high affinity receptors on the enlarged T-cells leading to rapid internalization of IL-1.The IL-1 readily induces RNA and protein synthesis of the responsive T-cells. The cell enlarges to a blast like appearance. Mechanisms of fever induced by recombinant human interferon Certain symptoms of infections, such as fever, muscle pain and "flu-like symptoms", are also caused by the production of IFNs and other cytokines [31].

Research on fever or pyogenic effect

It is the toxic effect produced by the smallest dose of endotoxin. As little as 0.002 micro gram endotoxin per Kg body weight injected intravenously in a highly susceptible species such as rabbit or man, causes within 15 mints an elevation of body temperature that lasts for several hours. The action of the endotoxin (Exogenous pyrogen) is to cause polymorphic leukocytes, macrophages and perhaps other tissue cells to release a small molecular protein which passes via blood to, and acts on the thermoregulatory center in the hypothalamus of the brain. If a small pyrogenic doses of endotoxin are injected on several successive days, a state of tolerance to their effects is produced.Interleukin-1 appears to be a protein with a molecular weight of 15,000 and an isoelectric point near 6.9.It is inactivated rapidly by Ph above 8.0 or heat and is neutralized by sulfhydryl-reducing agents. It induces no tolerance when administered repeatedly and its activity is greatly augmented when injected directly into hypothalamus.IL-1 can stimulate proteolysis by increasing the production of prostaglandin E2(PGE2). Cyclooxygenase inhibitors can prevent this. It is possible to demonstrate some beneficial effects of fever on the control of infection in isolated instances. For example, antibody production and T cell proliferation are more efficient at elevated than at normal body temperatures Pyrexia as an instrument of hindrance or resistance Fever is a response of the body to microbial infection. It is a part of the body's normal defense. Indeed, antipyretic drugs are very widely used spontaneously by patients and the prescriptions of physicians. Fever can possibly influence resistance to infection in several ways. The microorganisms themselves may be sensitive to temperature or may fail to elaborate their toxins. Alternatively, the various cellular and humoral mechanisms of the body's resistance may be enhanced by a rise of temperature. There are several examples of microbes which are killed in vitro at the temperature of 40-42 degrees c, which are attainable by pyrexia in man. In two human infections the evidence for the efficacy of artificial fever therapy is excellent. This is the case in urethritis, arthritis and ophthalmitis due to gonococcus and in neurosyphilis due to *Trypanosoma pallidum*.

Many studies have been made in experimental animals of the pyrogenic action of bacterial endotoxins. As little as 0.01 microgram per kilogram body weight will elicit a definite febrile reaction in the rabbit and man. These endotoxins when administered into bloodstream act mainly by causing the release from the recipient's own cells of an alpha- globulin with pyrogenic activity. One important source of this endogenous pyrogen" is the polymorphonuclear leukocyte, but other cells must also be involved since leukopenia animals show little impairment of their pyrogenic reaction to endotoxin. Endogenous pyrogen appears to be released because of damage to stimulation of the susceptible cells Clinical features of Lassa fever Characterized by high fever, intercostal myalgia, bradycardia, a low blood pressure and leukopenia.

Adherent yellow exudates in pharynx are particularly characteristic. In severe cases liver and renal failure, electrolyte imbalance, hemorrhage and acute circulatory failure develop.

Marburg and Ebola After an incubation period of 5-9 days, the illness presents suddenly with fever, myalgia and diarrhoea By the 4th or 5th day, the faces become inflamed and a bright red, follicular rash appears on the extensor surfaces of the limbs. About the sixth day, in severe case bleeding associated with thrombocytopenia starts usually in the gastrointestinal tract. Dengue fever Classical dengue fever usually affects older children and adults. It is followed by fever, headache, and pain in muscles and bones. The fever is biphasic (Saddleback) Incubation is 5-8 days. The maculopapular rash generally appears in 3 or 4 days. The febrile illness lasts for about 10 days. The dengue hemorrhagic fever (DHF)and dengue shock syndrome (DHF) remains mostly confined to children of 5-10 years of age. It is seen in patients previously infected with the dengue virus.

Dengue fever is continuous or "saddleback" with a break on 4th or 5th day and then recrudescence; usually lasts 7-8 days. Yellow fever the incubation period is 3-6 days. The dangerous aspects of the disease, is high fever, intestinal haemorrhage (Black vomit blood altered by the gastric juices); Albunuria, liver damage etc are associated with this stage of the disease Chikungunya It is the cause of an acute dengue like pyrexia of sudden onset, associated with intense joint and muscle pains and a rash. The name of the virus derives from an African language "The things causing bending up" *O'nyong-nyong Viruses* First appeared in Uganda. It is similar to chikungunya. Mosquito borne. Characterized by high fever, joint pains West Nile virus Most infections occur in children. and are inapparent. or clinically mild epidemics affecting all ages have occured in Israel. Affected people showed fever, sore throat, and lymphadenopathy and sometimes rash. Rift valley fever Endemic in sheep and cattle in South Africa. In man produce mild fever. Man is most commonly infected by handling sick or dead animals but sometimes by mosquito bite. Kyasanur Forest Disease (KFD) KFD virus appeared as a new disease in the Kyasanur forest in Mysore district, it is characterized by mild fever, headache, conjunctivitis, vomiting and diarrhoea. Recovery from attack is slow and fatality may be 10% OMSK haemorrhagic fever (OHF) It occurs in USSR and in Romania. Clinical disease is like KFD. Patients suffer from fatal infection and, infected by musk-rats Colorado tick fever It occurs in the West USA and in Canada.

Often it is inapparent or mild infection but may be severe biphasic fever with hemorrhage and encephalitis complications in children Sand-fly fever (SF) It occurs in Midterranian basin through the central USSR to India Transmitted through sand flies. The infection in man may be severe fever characterized by myalgia, conjunctivitis and retro orbital pain (32) Pathology The main lesions in yellow fever are found in the liver and kidneys but haemorrhages may take place into many organs. Characteristic inclusions "councilman bodies and Torries bodies are usual. The kidney shows acute tubular necrosis. Rift valley fever resemble dengue fever or fever with retinal changes with haemorrhages and jaundice or with meningoencephalitis. Dengue is characterized by fever and intense backache and generalised pains especially severe in the orbital and periarticular areas.painful movement of the eyes, photophobia, vomiting, anorexia, prostation, insomnia and depression are often features of the disease. Lassa fever lasts between 7-17 days. In severe cases liver and renal failure, electrolyte imbalance, haemorrhage and acute circulatory failure develop. Marburg and ebola viruses have a unique identical structure but anti genetically distinct. After an incubation period of 5-9 days, the illness presents suddenly with fever, severe myalgia and diarrhea. By the 4 or 5th day fauces become inflamed and rash appears on the exterior surfaces of the limbs and spread to the trunk and face. In severe cases bleeding associated with thrombocytopenia starts usually in the gastrointestinal tract. The virus also attacks the brain, lungs and kidneys [32,33].

Laboratory Diagnosis

Rapid flow ICT assays available for the qualitative detection of anti DENV IgM, IgG, IgA and NSI Antigen in human bold require minimum time, technical expertise and infrastructure [34] The detection capability of these assays for different viral markers varies in different geographical settings. A standard ELISA is commonly used as a comparator to evaluate rapid assays [35] Laboratory features include leucopenia, neutropenia, thrombocytopenia, elevated Alanine Aminotransferase (ALT)or Aspartate Aminotransferase (AST) The diagnosis can be confirmed by sero conversion of IgM or a four-fold rise in IgG antibody titres Serological tests may detect cross-reacting antibodies from infection or vaccination against other flaviviruses including yellow fever virus. Japanese encephalitis virus, and West Nile virus. Detection dengue virus RNA by PCR in blood or CSF is available in special laboratories [36] ELISA is used for the detection of IgM antibody. A strip of an immunochromatographic test for IgM is also available for rapid diagnosis. IgG antibody appears later than IgM titer in paired sera taken at an interval of ten days or more is confirmatory. ELISA is used for detection of IgG antibody Immunochromatographic test is available for detection of NSI antigen. It is a rapid test and detects antigen on the first day of fever before antibodies appear. It takes 15 minutes for isolation of the virus [37].

Yellow fever virus may be recovered from the blood up to the fifth day of the disease by intra cerebral inoculation of mice Nt antibodies develop early even in severe and fatal cases CF antibodies are rarely found after mild infection or vaccination with the attenuated live 17 D strain. In sandfly fever, the diagnosis is made usually on clinical grounds It may be confirmed by demonstrating a rise in antibody titer in paired serum specimens by Nt or HI tests. Colorado tick fever virus may be isolated from whole blood by inoculation of suckling mice Virus may persists for two weeks in blood. Specific Nt and CF antibodies appear in the second week of illness and persist for years. West Nile virus can be recovered from blood taken in the acute stage of the infection on paired serum specimens CF, HI, and Nt titer rises may be diagnostic Nt antibodies persist longer than CF antibodies [38]. Treatment for Viruses associated with pyrexia the presence of clinically apparent dengue virus (DENV) infection has increased significantly in recent decades. Since there is no specific treatment to dengue virus, patients are solely managed by supportive therapy. Moreover, prevention of dengue is challenging

for health authorities despite the exhausting efforts taken in the dengue endemic countries including Sri Lanka. Through the recombinant tetravalent vaccine (Dengvxia) registered for use in Mexico in 2015 [39] Treatment is supportive. Paracetamol is the preferred antipyretic agent. Mild sedation is required to control pain. Fluid replacement and appropriate management of shock and organ dysfunction. which is a major determinant of morbidity and mortality. With intensive care support, the mortality rate is 1% less. Aspirin should not be given due to bleeding risk. Glucocorticoids have not been shown help no existing antivirals are effective.

Strict isolation and general supportive measures, preferably in a special unit, are required for the treatment of Lassa fever. Ribavirin should be given by slow IV infusion in a dose of 32 mg/Kg. This dose should be followed by 16mg/kg every 6 h for 4 days and then by 8 mg/kg every 8 h for 6 days. Inactivated Lassa virus vaccines failed in preclinical studies, but several promising vaccine platforms are currently under experimental evaluation [40] Marburg and Ebola virus, treatment consists of supportive measures, replacement of blood and the management of complications. Immune plasma may be beneficial if given at an early stage. No vaccine is available. No specific treatment for yellow fever the patient should be nursed under a mosquito net for the first four days of the illness because the blood is infectious. Dehydration should be corrected by intravenous glucose saline and blood transfusions should be given if blood loss is severe. The adequacy of blood transfusion and fluid therapy is best monitored using indwelling right atrial catheter and assessed by clinical response.

Prevention of viruses associated with pyrexia

The dengue fever is caused by the bite of one of the many types of mosquitoes in the genus Aedes Aegypti, which has white stripes on their bodies and legs. It is caused when the mosquito has previously bitten a person who was infected. Control of stagnant water using mosquito nets is highly useful in malaria control but Aedes aegypti bites during the day. The ability to predict epidemics and to put in practice public health and clinical needs to deal with such surges in demand would be a major advance with ongoing difficulties in the development of an effective and balanced vaccine to all four dengue serotypes; concerted efforts are needed to address this important global health threat [41] Yellow fever can be prevented by single vaccination with 17 D non-pathogenic strain of virus, available at internationally recognized centers ,given full protection for at least 10 years, the period of validity of the vaccination certificate. Ten days after the vaccination adequate antibodies are present in the blood and the certificate of vaccination becomes valid. The vaccine does not produce appreciable side effects in adults, unless they are allergic to egg protein, when desensitization may be necessary. The administration of convalescent immune plasma has been followed by recovery and is therefore recommended for prophylaxis after accidental exposure to infection for the Lassa fever Conclusion The occurrence of recurring outbreaks every 3–5 years with an increasing number of cases over time shows the transition from an endemic-epidemic state to a highly endemic state in recent years. Dengue remains to be an important health problem affecting geographies, across the globe. Few serotypes are more dangerous. Rapid diagnosis and serotyping remain the key for better patient management and prevention of disease spreading in the community. Highly sensitive, specific, and rapid CDC real time PCR assay. It is a promising tool among all available molecular diagnostic methods [42] The only control measure currently available is vector control [43].

Challenges

Dengue begins suddenly, with more benign symptoms at first but which may get severe with time. Dengue is one of the world's most important emerging diseases as the global incidence continues to rise and new areas of the world experience explosive epidemics, there are major challenges ahead. There have been recent advances in our understanding of immunopathogenesis and pathophysiology plus identification of the therapeutic targets, which should lead to urgently needed treatments. The development of an effective and safe vaccine to all four dengue serotypes and better control of the vector are needed to address this important and growing global health threat. Colorado tick fever can be prevented by avoiding tick infested areas, and by using protective clothing or repellent chemicals. Rift valley fever causes enormous losses of sheep and cattle, and thousands of human cases occurred vaccination of livestock with available killed or live attenuated vaccines should prevent transmission to both human and animals. An excellent attenuated live vaccine is available in the 17D strain.

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