GLOBAL PREVALENCE OF DENGUE VIRAL INFECTION, ITS PATHOGENESIS DIAGNOSTIC AND PREVENTIVE APPROACHES

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ABSTRACT

Dengue viral infection (DVI) is amongst a big Global health challenges. The clinical manifestations of disease ranges from subclinical Dengue fever (DF) to the complicated dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). Reason behind this is the absence of specific tetravalent vaccine and the anti virals. The mortality rate with the infection might exceed upto 5%. Therefore, there is a dire need to emphasize the adoption of preventive strategies and to control the vector Aedesaegypti mosquito population. Moreover, the regular cross sectional, age stratified, serological surveys are the surveillance tools for monitoring the impact of Dengue prevention/ control and a better way to plan for potential epidemics.

Keywords: Dengue Fever Global Prevalence, Dengue Pathogenesis, Dengue Infection Diagnosis

INTRODUCTION

Dengue Fever 'ABreak Bone Fever'
A Spanish word 'dengue' means Fastidious or Careful. An American physician Benjaman Rush first gave Dengue fever a name Break Bone fever or Bone Crush Disease. This is attributed to the major complications of disease i.e. myalgias and arthralgias (Harper, 2008; Reed, 2008). According to the WHO report it is amongst the most common causes of arboviral diseases worldwide (Rathor, 1998; Heyman, 2008)**.** *Aedes aegypti* is the principle vector in the transmission of disease. This special mosquito is well adapted to humans and prefers to live in clean surroundings in close proximity to clean human surroundings (Heyman, 2008).

Dengue Virus and Serotypes
It is the most common cause of arboviral diseases worldwide (Yasmashiro, 2004). It consists of four serotypes. DEN 1, DEN 2, DEN 3 and DEN 4.These serotypes were classified by Albert Sabin in 1944. Infection with DEN viral serotypes has been a major concern in DEN endemic areas worldwide. The reason behind this is the co circulation of all the four serotypes (Heyman, 2008; Gubler, 1998).

Pathogenesis
These serotypes are responsible for the production of serotype specific IgG antibody mediated protective immunity following the first infection (Gubler, 1996). There are two types of serological responses in Dengue viral infected patients i.e. primary and the secondary ones. The response is dependent upon the immunological status of the infected individual. A primary response is seen in those who are not immune to flaviviruses, while a secondary response is seen in those who had previous flaviviral infection. It will be responsible for the pathogenesis of DF, DHF and DSS. This primary response can be very well differentiated from the secondary response by ELISA method for diagnostic purpose (Kumar, 2005).

Commonest Serotype
Previously DEN 2 serotypes were more common but recent studies have shown the increased prevalence of DEN 1and DEN 3 serotypes (Lolekha, 2004; Khan, 2006).

Prevalence of DEN 2 And 3 Serotypes in Pakistan
In Pakistan DEN 2 serotypes predominates followed by DEN 3 serotype (US News 2010).

WHO Dengue Report about Pakistan
The WHO and US centers for disease control has considered dengue fever a major health threat for Brazil, Pakistan and India (CDC Report, 2013).

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Dengue in Pakistan

In 1994 first outbreak of DHF occurred at Karachi, Pakistan. In 1995, second outbreak occurred in Baluchistan. In 2002, the educational programmes for *Aedes aegypti* mosquitoes were established (Almani, 2008). In 2003, 10 cases were confirmed along with 4 deaths at Haripur (Qasim, 2008). In Rawalpindi, from September to November 2008, 49 positive cases detected. Out of which 23 reported at BBH and 26 at HFH (Edelman, 2007).

Dengue A Global Health Problem

The absences of specific vaccine and anti viral treatment of DF are the main reasons for making it a global health problem (Hapugoda, 2007; Gathatry, 2009).

Dengue Vaccine

It has been very well analyzed from the current study that the final winning goal of the fight will be the discovery of DV vaccine. The vaccine must be tetravalent to provide immunity against all 4 circulating serotypes. Thus reducing the chances of cross reacting antibodies formation. Researchers have discovered dozens of areas on vector Aedes mosquito and about 42 dengue specific host factors. These can serve as targets for new kinds of drugs and vaccines (Hastlead, 2002). Novartis and Sanofi Aventis are devoted to produce a long awaited vaccine against DV. It will be available by the end 2012 or 2013. This vaccine contains proteins from all the 4 viral strains. The vaccine is still under trials and has proven effective result against all the 4 strains of DV when given and tested on monkeys. (Sanofi Aventis, 2009; Serafini, 2007).The vaccine design will be a promising strategy to prevent Dengue infection (Evans, 2009).

Dengue a Growing Threat

Dengue viral infection is becoming a growing threat to the population of developing world (Senanayake, 2006). DF is a terrible viral disease. It has involved many tropical regions of the world. It has been estimated that about 40% of world population is at the risk for this infection (Durand, 2003).

Endemic Viral Disease

DF is an endemic viral disease affecting the tropical and subtropical regions around the World, especially in urban and semi urban areas. The global prevalence of DF has grown dramatically in recent decades. It is now endemic in more than hundred countries of Africa, America, Eastern Mediterranean, South East Asia and the Western Pacific (Focks, 2000).

Global Epidemiological Pattern of Dengue

The epidemiology of DF has been drastically changed, resulting in the increased incidence of disease worldwide along with the worsening of clinical symptoms. The course of epidemic is dependent upon the rate of contact between the host, the infecting vector and the threshold theory. This theory states that the introduction of few infected individuals in the community will not give rise to an outbreak unless the density of vector exceeds a certain critical level (CDC Report, 1980).

The incidence of DHF has dramatically increased in South East Asia, South Pacific and America during the last 25 years. The first epidemic of DF was notified by American Government in 1981 at Cuba. The second occurred at Venezuela in 1989 - 90 (Srivastava, 1990). In 1980, several cases of DF were identified in Southern Texas. This was found to be associated with epidemic Dengue in adjacent states of Mexico (Effler, 2005). In 1990, Indian Government disclosed the first epidemic of DF (Noisakran, 2008).The Hawaii government notified first DF epidemic in 2001(Ewathorn, 2007).

Mortality Rate from DHF/DSS

The death rates associated with DHF/DSS is approximately 5% predominantly in children under 15 years (Clark, 2005).

Dengue Shock Syndrome

DSS is associated with the high morbidity and mortality rates. This is especially in cases of prolonged shock, massive bleeding and hemoconcenteration more than 22%. The morbidity and mortality rates can be decreased by early diagnosis and prompt management of the condition (Siqueira, 2005).

Estimated Financial Losses with DF/DHF

DF and DHF is a substantial health burden in Thailand population. The financial losses were observed to be 61 US dollars per family. This is more than the average monthly income of Thailand population. The results of the study indicated that dengue prevention, control and

research must be given equal importance as that of diseases currently given priority (Itoda, 2006).

LITERATURE REVIEW

Predisposing Factors

The contributing factors in the predisposition of disease includes the age of patient (Smith, 2005), immune status, type of virus infecting, humid climates especially rainy season and temperature $>20^0$C. The residents returning from overseas countries where dengue is endemic, increase in population growth, unplanned urbanization, increase in the international trade and increase in air travel. All of these provide an ideal way of transporting virus to new areas (Hastlead,2002;Smith,2004). These factors despite having vector control programmes and public awareness contributes to the outbreak in several urbanized areas (Rannos, 2008). Unplanned urbanization is one of the important reasons for the persistence of infection in many tropical and subtropical countries (Nakamura, 2009). The discarded waste tires and buckets are the favorite sites for proliferation of *Aedes aegypti* mosquito population (Guzman, 2004).

Lab Findings in Primary Infection

The initial lab diagnosis of DF includes the changes in blood peripheral film i.e. thrombocytopenia and leucocytopenia. While on bone marrow examination extreme plasmacytosis and haemophagocytosis are also seen (Wichman, 2006).

Methods for DV Isolation

An appropriate, rapid and easily accessible diagnostic method will be useful for epidemiological surveillance, control, and better management of diseases (Khanna, 2004). There are three important approaches for DV isolation: a; Serological tests. b; Viral isolation. c; Molecular tests. Theserological tests include the Haemagglutination Inhibition (HI), Complement Fixation test (CF), Neutralization tests (NT), IgM and IgG ELISA and Indirect Immuno Fluorescent Assay (IFA).The Viral Isolation includes the inoculation of mosquito cell culture, and inoculation of mammalian cell cultures. The Molecular analysis includes the test for nucleic acid hybridization, RT- PCR and DF Virus RNA detection (Hastlead, 2002).

Serological Diagnosis

The identification of anti Dengue antibodies is the most reliable method for diagnosing DF. These tests are cost effective, rapid, easily available and accurate for the diagnosis of DF. Sensitivity and Specificity Of ELISA: ELISA is considered to be a highly sensitive and specific method for the diagnosis of DF. It is 93.3% specific for DF virus (Kao, 2005).

Strategies for Disease Control/Prevention

The disease control and prevention is mainly focused on vector control activities and the surveillance that incorporates country's participation (Takhaynpuya, 2006).

Pharmaceutical Trials to Discover anti- DV Treatment

Studies on ribavirin and mycophenolic acid have shown that there is 5 fold increase in the defective viral RNA production with each drug (Fisher, 2005).

Dengue Prevention and Control

Excellent daily surveillance and coordinated correspondence between administration, epidemiologist and infection disease units provide a proactive approach for the prevention and control of disease in specific regions of the world (Egger, 2008).

Importance of Seroprevalence Studies

Moreover, the regular cross sectional, age stratified, serological surveys are the surveillance tools for monitoring the impact of Dengue prevention and control. It also helps to plan for potential epidemics. Most countries throughout the world have poor surveillance capabilities for the detection of both i.e., Dengue and the vector Aedes mosquito population. So there is an increased need of such studies. Thus, there is an immediate requirement of time to assess the Aedes mosquito population breeding sites especially in different surroundings .Due to relative ease and low cost, age stratified seroprevalence surveys have proven to be a useful tool in the surveillance of directly transmitted diseases (Egger, 2008).

To reduce Dengue in our country the National Dengue control programmes must follow all WHO recommended Dengue control guidelines. The important focused points in WHO guidelines are the public health

education, community participation, detection of breeding sites, environmental management by reactive insecticide fogging, geo referenced entomologic and clinical surveillance systems. The local, regional and National level efforts are required to control this disease. Moreover, similar researches must be encouraged on large scales in different cities of Pakistan.

CONCLUSION

Thus, by seroprevalence studies, strictly adhering to WHO guidelines and recommendations, policies regarding screening, vector control activities and health education awareness campaigns, along with community participation should be established to reduce the morbidity and mortality rates.The resultant of all this will successfully serve as an epidemiological tool in early warning system for DF potential epidemics.

Above all the final winning goal of fight will be the discovery of DF vaccine or specific antiviral agents. Otherwise dengue will grew up and soon take an epidemic proportion in our country.

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