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REVIEW ARTICLE OPEN ACCESS

Dengue Viral Infection and Necessity for Screening Patients Having Pyrexia of Unknown Origin

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Abstract

Dengue Viral Infection (DVI) is an emerging global health problem infecting about 50-100 million people annually world wide. More than 2.5 million people have dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). *Aedesaegypti* is the principal vector for disease transmission while humans are the main reservoir. The clinical manifestations range from self limited Dengue fever (DF) to complicated and fatal outcomes, DHF and DSS. DF is prevalent in more than 100 countries of the world. More than 2.5 billion people of the World's population are residents of Dengue endemic area. According to one reported study the prevalence of DF in Pakistan is 29%. Similarly one study result carried out in India has shown 78% prevalence of DF. In Mexico the one published seroprevalence study showed 79.6% prevalence of DF. A review/analysis report of Gynecological and Obstetrical survey from 30 published studies has shown 64% transmission rate of DF from a mother to a child. The study results carried out in Jamaica has shown an increased in the prevalence of DF in seen in less than 1year and more than 60 years. The mortality rate with DHF is 33%. While in less than 15 year of it is 5%. This can be only reduced with early/ accurate diagnosis and the prompt management of the condition. Absence of specific vaccine and anti viral is responsible for making this infection as a global health problem. The US government has spent 15 million US dollars for the establishment and discovery of specific DF treatment. The study carried out in India has shown the median cost for treatment per patient about 432.2 US dollars. It is 4 times in case of private health sectors. The proposed review article will highlight the incidence of dengue infection in patients having PUO (pyrexia of unknown origin). It will be a guide for the clinicians to consider DVI in their list of differential diagnosis of PUO. Moreover it will be helpful in establishing the screening policies for DVI in PUO. The resultant of all of this will improve the life quality of PUO sufferers. It will be useful to reduce the increased financial burden due to PUO missed diagnosis and management in under developed countries like one of ours.

Keywords: Dengue viral infection, pyrexia of unknown origin, screening for PUO

Introduction

Break Bone Fever

The word dengue has been derived from a Spanish word meaning *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 (1,2,3). Dengue virus belongs to genus flavivirus (4). According to the WHO

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report it is amongst the most common causes of arboviral diseases worldwide (5,6).

Vector of Disease

Aedesaegypti 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 humans. *Aedesaegypti* is the small sized mosquito in comparison to the other mosquitoes. It is black colored with white stripes on head and body. There are specific white rings on the legs. *Male Aedesaegypti* population is harmless to humans and usually lives on fruits. *Female Aedesaegypti* are the ones responsible for disease transmission. It sucks blood from one person and transmits to another by biting.The infection develops within 24-30 hours of biting. This pathway between man-vector-man makes a triad of disease (5). *Aedesalbopictus* is a lesser vector of dengue viral infection. Few cases with this vector have been recorded in Pakistasn and USA (5).

Pathogenesis of Dengue Infection

Dr.Albert Sabin in1944 isolated and detected four serotypes of DV. DEN 1, 2, 3 and 4 are the well known ones for DVI. These serotypes are responsible for the production of serotype specific IgG Ab mediated protective immunity following the first infection(7). *Extrinsic Incubation Period:* During these period mosquitoes acquire virus while feeding on the viremic humans. Viral replication starts in the salivary glands of *Aedes.* This is called as Extrinsic I/P. The mosquitoes remain infected until 65 days of their lifespan. *Intrinsic Incubation Period:* There are two types of serological responses seen in DVI patient i.e primary and the secondary one. A primary response is seen in those who are not immune to the Flaviviruses. While secondary response is seen in those who had previous flaviviral infection. Thus responsible for pathogenesis of DF, DHF and DSS (5,8).

Dengue Virus Genotype And Virulence

In Malaysia DEN 4 serotype is the most common disease causing one (9). While in Pakistan DEN 2 serotypes predominates followed by DEN 3 serotype (10). The infection with any one serotype provides the immunity against that specific serotype (11). Ab produced in result of infection with any serotype usually provides the homotypic immunity (12).

LITERATURE REVIEW

Dengue In Pakistan

In 1994 first outbreak of DHF occurred at Karachi, Pakistan. In 1995, second outbreak occurred in Baluchistan. In 2002, educational programmes for *Aedesaegypti* mosquitoes were established (13). In Rawalpindi, from September to November 2008, 49 positive cases were detected. Out of which 23 reported at Benazir Bhutto Hospital and 26 at Holy Family Hospital (14).

Predisposing Factors

The immune status, age of patient, type of virus infecting, climatic change, 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 (15). Moreover lack of awareness and knowledge especially in low socioeconomic class contributes to the spread of disease (16). The WHO report of the year 2007 had highlighted DF a great threat for travelers (17). The appropriate education to the travelers can be helpful to reduce arthropod borne diseases (18).

Dengue A Global Health Problem

DF is prevalent in more than 100 countries of the world (19). More than 2.5 billion people of the World's population are residents of Dengue endemic area (20). Currently there is no vaccine or specific anti viral drugs/ injections available for the treatment of DF. Thus, making it a global health problem (21,22).

Commonly Affected Age Groups

A study report on Jamaican population has shown that DF usually affects less than 1 year and more than 60 years of age group (23). A study in Bangladesh concluded that adults are frequently infected by DV (24). WHO report has shown that DF is a febrile illness which mostly affects the infants, young children and the adults (25).

Vertical Transmission of DVI

A case report in Bangkok has shown that DVI can be vertically transmitted from a mother to 1 day old infant (26). Another study carried out in Kuala Lumpur has shown that vertical transmission rate of DF is 1.6% (27). A systematic review report of 30 published studies by gynecological and obstetric survey 2010 has shown vertical transmission rate of 64% (28).

Clinical Manifestations of DVI

These ranges from self limited DF to DHF and DSS (29). DF/DHF are amongst important differential diagnosis in an undifferentiated febrile illneses (30). The fever could be of biphasic pattern (31). WHO definition of DHF requires filling of criteria: a; fever,bladder problem, constant severe headache, dizziness and loss of appetite. b; Haemorrhagic tendency, i.e. positive tourniquet test, spontaneous bruising, bleeding from mucosa, gingival, injection site etc, menorrhagia, bloody vomiting, malena or bloody diarrhea. c; Thrombocytopenia i.e. less than 100,000/mm3 platelets. d; Hemoconcenteration i.e. evidence of plasma leakage and hematocrit >20% of expected following I/V fluids, pleural effusion, ascities or hypoproteinemia (32,33,35). DSS is defined as DHF plus weak and rapid pulse, narrow pulse pressure <20 mmHg, cold and clammy skin and restlessness (1-3).

Mortality Rate of DHF/ DSS

It is 5% in less than 15 year of age group (34). While the estimated overall mortality rate with this infection is 33% (35). The mortality rates can be decreased by early diagnosis and prompt management of the condition (36). A study carried out on the citizens residing in Puerto Rico, United States, has shown that the infants and 10 to19 years of age group are amongst those who usually harbor the severe outcomes of DF (37).

DVI and PUO

A study result carried out in Singapore on Chinese migrant workers hospitalized due to febrile illness since a month. The serological results have shown the prevalence of acute Dengue in 10% of patients. The most common serotype was DEN 2 (38). Another study results carried out in United Kingdom had shown that DVI can present as undifferentiated fever (39). A study carried out on children between 6 months to 12 years in Lucknow, India has shown that DVI can cause undifferentiated febrile illness (40). The Cuban Government had declared two Dengue outbreaks showing the presence of febrile illness as initial presentation in 3.2% of the total diagnosed cases (41). In Thailand population the estimated prevalence of DF in patients having PUO is 40.8% (42).

Diagnosis of DVI and ELISA

Serologiacal tests, viral isolation and molecular level detection are the three options for DV detection (44). ELISA is considered to be 99.2% sensitive and 96.2% specific for DF virus IgG detection (45). The Dengue virus IgG antibodies in the serum are not affected by the duration of storage (46).

Cross Reacting Antibodies Formation

The high degree of cross reactivity between flaviviruses can result in false positive serological results. The booster for Yellow fever immunization is 10 years, for Tick borne encephalitis is 3 years and for Japanese encephalitis is 2 years (41,47,48).

Dengue Prevention

The laboratory based surveillance and daily correspondence between epidemiologists and infectious disease units will provide a proactive approach for the prevention and control of disease in specific regions of the world (49).

Conclusion

One of the early presentations of primary dengue viral infection is PUO especially in less than 18 years of age. So that the Government should mainly focus on the particular age group. This study will be helpful for the clinicians to consider DVI in their list of differential diagnosis of PUO.

Recommendations

Screening of Dengue viral infection should be done in patients having pyrexia of unknown origin.

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