Review Article

Clinical and Oral Implications of Dengue Fever: A Review

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Abstract:
Dengue is a viral infection with fatal potential complications. It is also called as break-bone fever. Worldwide dengue infection is the most common mosquito-borne viral disease. It is caused by vector *Aedesa egypti* and represents a major public health issue in more than 100 tropical countries. The word dengue is obtained from Swahili phrase Ka-dinga pepo meaning "cramplikeseizure." Dengue viral infections are characterized by abrupt febrile illness, but can also lead to significant morbidity and mortality. Hence, it requires an early and correct diagnosis. Gingival bleeding is the most common oral manifestation of dengue infection. Although oral lesions are uncommon in dengue infections and if manifested, may be mistaken for bleeding disorders. This review emphasizes the significance of oral lesions as it may be the early indicators of dengue hemorrhagic fever.

Key Words: Dengue, oral manifestations, platelet count

Introduction

Dengue fever (DF) is a severe flu-like illness transmitted among humans by the mosquito *Aedesa egypti* and is seen mostly in the rainy season[2] affecting all the age groups.[1] The infection of Dengue virus (DenV) belongs to family *Flaviviridae* and has four serotypes in recent decades, the global distribution in tropical and subtropical areas have been and over 2.5 billion people live in areas where dengue is endemic.

The first dengue-like illness to be documented in India was in madras and Calcutta was the first city to report virological epidemic of DF.[3] In recent times, the cumulative dengue diseases burden has attained an un paralleled proportion with upsurge in the magnitude of human population at risk. Complex pathophysiological, economic, and ecologic problems are highly presented in dengue infections.[4] Oral lesions are rare to occur in dengue infection and if present, are often mistaken for bleeding disorders. Hence, oral manifestations in dengue infection are given significant importance in making an early and accurate diagnosis.

Etiopathogenesis

Various theories have been proposed for the cause of dengue infection that includes replication of the virus occurring primarily in the macrophages[5] and infection of the skin directly by the virus.[6] Interaction of the virus with the host inducing immunologic and chemically mediated mechanisms.[6] There are four single-stranded RNA, immunologically related, DenV serotypes (DenV-1 to DenV-4), with a viral genome approximately 10 kB in length composed of 10 genes. Three of these encode structural proteins and seven encode nonstructural ones. Infection by any of them is thought to confer lifelong immunity against variants of the same serotype, but only partial and transient cross-protection against infections caused by other serotypes.[7,8] It is known that the DenV enters the host organism via the skin when an infected mosquito takes its blood meal. However, the most severe clinical presentation during the infection course is not accompanied by a high viral burden. These symptoms occur following the rapid clearance of the virus from the host organism, suggesting that the humoral, cellular, and innate immune responses of the host are associated with the pathogenesis of dengue infection.[9]

The immune pathogenic events of dengue infection are usually related to disruptions in endothelial microvascular permeability and thrombo regulatory mechanisms, leading to an increased rate of protein and plasma loss. It has been postulated that endothelial cell activation caused by monocytes, T-cells, the complement system, and various inflammatory molecules mediate plasma leakage, which is linked with useful rather than damaging effects on endothelial cells. Thrombocytopenia may be associated with alterations in megakaryocytopoiesis, elicited by the infection of human hematopoietic cells and impaired progenitor cell growth, which result in platelet dysfunction, destruction, or consumption, leading to significant hemorrhages.[10,11]

An abnormal immune over-stimulation occurs after DenV infection which not only impairs the immunity to clear the virus, but also results in increased production of cytokines that affect, endothelial cells, monocytes, and hepatocytes. There is abnormal production of autoantibodies to endothelial cells and thrombocytes. A molecular imitation occurs between thrombocytes or endothelial cells and DenV antigens. Hemorrhage occurs due to DenV-induced vasculopathy and coagulopathy. An association between virus serotype and severity of infection in pediatric patients was demonstrated by Vaughn *et al.*, but there are no available data concerning this association in the adult population.[12]

Clinical features

Dengue viral infection may result in illness varying from a mild undifferentiated fever to severe life-threatening forms.

There are four serotypes of DenV:
- Undifferentiated febrile illness or viral syndrome
- Classic DF
- Dengue hemorrhagic fever (DHF)
- Dengue shock syndrome (DSS).

Undifferentiated fever

This frequently follows a primary infection but can also occur during the initial phase of a secondary infection.

DF

The symptoms usually start with a sudden onset of high fever lasting for 4-8 days. Intense headache, retro-orbital pain, fatigue, muscle and joint pain, loss of appetite unpleasant metallic taste in mouth, vomiting, diarrhea, and abdominal pain are the other symptoms. Manifestations of the skin commonly occur as rashes on the face, extremities and spreads to the trunk. In few patients, a severe erythematous prototype with islands of normal skin is seen as macular, papular rash. The other features, which could be present are minor epistaxis or bleeding gums, heavy menstrual periods, petechiae, and gastrointestinal bleeding. Several individuals with DF have been reported with a positive tourniquet test.

DHF

Generally follows a secondary infection. It is characterized by pyrexia, hemorrhagic phenomena, hepatomegaly and features of circulatory failure.

DHF is classified into four types according to severity:
1. No shock, only positive tourniquet test.
2. No shock, spontaneous bleeding excluding positive tourniquet test.
3. Shock.
4. Profound shock with unstable blood pressure and/or narrow pulse pressure.

The clinical progression of DHF is alienated into three stages namely febrile, leakage and convalescent stages. The febrile stage begins with rapid onset fever. The pyrexia is intermittent, high grade (usually >39°C), and associated with chills and rigors. Bleeding manifestations and rashes appear in the initial febrile stage. The fever persists for 2-7 days and then falls to usual or subnormal levels when the patient recuperates or progresses to plasma leakage stage. Patients remain ill, despite normalization of temperature.

In severe cases with high plasma leakage, frank shock is apparent with low pulse pressure cyanosis, hepatomegaly, pleural effusions, pericardial effusion, ascites and in some cases a severe ecchymosis and gastrointestinal bleeding followed by epistaxis. During convalescence period, decreased heart rate and confluent petechial rashes, erythema and pallor are seen. The threatening stage in DHF is signs of circulatory failure and hemorrhagic tendencies. Hematological investigations usually show platelet count, $\leq 100,000/mm^3$ as an evidence of a vascular leak syndrome.

WHO definition for DHF: Recent fever lasting for 2-7 days, occasionally biphasic, hemorrhagic tendencies evidenced by at least one of the following:
- A positive tourniquet test
- Petechiae or purpura
- Mucosal bleeding
- Hematemesis, melena
- Platelet count $\leq 100\ 000/mm^3$.

Objective indication of plasma leakage initiated by increased vascular permeability is demonstrated by at least one of the following: Elevated hematocrit, pleural or other effusion as in. ascites and low protein.

Dengue shock syndrome

Is defined as DHF associated with a weak rapid pulse, narrow pulse pressure, which is <20 mmHg, cold, clammy skin, restlessness, circumoral cyanosis and high mortality. Patients with DSS die due to progressively worsening shock and multi-organ failure and disseminated intravascular coagulation. The phase of shock is transient, and the patient promptly recuperates with right supportive therapy.[13,14]

Orofacial manifestations

Oral mucosa is affected in approximately 30% of patients with dengue viral infections and more often in patients with DHF than with DF.[15] The oral manifestations prominent in dengue viral infections are erythema and crusting of lips, tongue and small vesicles on soft palate. Chadwick *et al.*[16] reported higher percentage of mucosal involvement with scleral injection (90%) and vesicles on the soft palate (>50%).[17] Amitbyatnal *et al.* stated occurrence of numerous hemorrhagic bullae on left sublingual mucous membrane as well as left lateral surface of the

tongue and floor of the mouth. They also reported the existence of brown color plaques with a rough surface on the buccal mucosa that showed bleeding on touch along with spontaneous bleeding from the gingiva and the tongue. Petechiae, purpura, ecchymoses and nasal bleeding have also been reported.[4] Mitra *et al.* reported that along with bleeding gums and hemorrhagic plaques, the tonsils on the both sides was inflamed. Xerostomia and the tongue coating has also been reported.[18]

Differential diagnosis: Differential diagnosis of DF and DHF are discusses in Table 1.

Disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, post-transfusion purpura and idiopathic or immune-mediated thrombocytopenic purpura, drug-induced Infectious mononucleosis, chikungunya viral infections, enteroviral infections, rickettsial infections, rubella and influenza.

Laboratory diagnosis
Confirmation of dengue infection is by serology or detection by virus isolation and by reverse transcriptase polymerase chain reaction. The timing of clinical course plays a major role in the Laboratory diagnosis of dengue.

Virus isolation and identification is a gold standard for diagnosing dengue infections. This procedure can simply be done using infected cell cultures obtained from plasma, serum or WBC, and this procedure is consistent, effortless and most rapid. In addition, it allows the recognition of numerous viruses in patients with concomitant infections with above one serotype.[14,19]

Serological diagnosis
Diagnosis of dengue infection can be performed using five basic serologic tests hemagglutination-inhibition, complement fixation, neutralization test, immunoglobulin M capture enzyme-linked immunosorbent assay, and indirect immunoglobulin G ELISA. Serologic diagnosis depends upon the increase in the titer of specific antibodies between acute- and convalescent-phase serum samples.

Viral serotypes
Reverse transcriptase-polymerase chain reaction (RT-PCR) provides a rapid serotype-specific diagnosis. This method is rapid, sensitive, simple, and reproducible.[14,19]

Immunofluorescence
De Andino *et al.* conducted a study on direct immunofluorescence involving the skin showed negative for the deposition of immunoglobulins and complement and for the presence of dengue viral antigen.[20]

Management
Non-steroidal anti-inflammatory drugs such as ibuprofen should be avoided. Fever is usually treated with paracetamol. Sponging is helpful in the early phase of infection, oral fluids given to the patients are increased, and in the presence of dehydration, intravenous fluids should be administered with follow-up hematocrit and platelet counts and this should be continued until patient recuperates.

Management of DHF
The mainstay of management is maintenance of fluid and electrolyte balance. A platelet count <100,000 and a >20%

Table 1: Differential diagnosis.				
Disease	**Etiology**	**Clinical features**	**Differential diagnosis**	**Management**
Disseminated intravascular coagulation	Infection/sepsis, trauma, obstetrics e.g., amniotic fluid embolism, pre-eclampsia and severe liver failure	Bleeding, organ damage due to ischemia caused by effect of widespread intravascular thrombosis, microangiopathic hemolytic anemia	Other consumptive coagulopathies like trauma, and major surgery, severe liver disease, thrombocytopenia	Primarily aimed at underlying cause, Fresh frozen plasma, cryoprecipitate and platelets, Established thrombosis treated by unfractionated heparin
Thrombotic thrombocytopenic purpura	Mediated by antibodies against ADAMTS-13 (A dis integrin and metalloproteinase and a thrombospondin type-1 protein)	Purpura, fever, microangiopathic hemolytic anemia, hemorrhagic infarcts as a result of intravascular thrombosis	Idiopathic thrombocytopenic purpura, Evans syndrome (former plus immunohemolyticanaemia)	Emergency plasma exchange, plasmapheresis with plasma replacement, glucocorticoids, aspirn
Chikungunya	Chikungunya virus, it's an alpha virus transmitted by *A. egypti*	Fever, severe arthralgia, chills and other symptoms like headache, photophobia, anorexia, migratory polyarthritis affecting small joints	Infections due to O'nyong-nyong virus, Ross-river virus, Sindbis virus	Symptomatic treatment
Rickettsial infection	Ticks, mites, lice and fleas	Initially-fever, headache, malaise, myalgia, maculopapular rash, neurologic disturbance, renal failure, hepatic injury and bleeding	For Early lesions-RMSF (fever, headache, myalgia without rash) include influenza, typhoid fever and later stages-meningococcal sepsis, leptospirosis.	Tetracycline -500 mg 6 hourly Doxycycline - 200 mg daily Chloramphenicol - 500 mg 6th hourly for 1 week
Rubella	Rubella virus, a toga virus	Rash, fever, lymphadenopathy, arthritis	Contact dermatitis, CMV infections, measles, toxoplasmosis	Symptomatic treatment Prevention by live attenuated rubella vaccine
Infectious mononucleosis	Ebstein–Barr virus, antibiotic induced rash (80-90% associated with ampicillin)	headache with malaise, severe pharyngitis, tonsillar exudates, palatal petechiae, periorbitaledema and splenomegaly	Acute infection with CMV, toxoplasma, HHV-6 and hepatitis viruses	Supportive measures with rest and analgesics
CMV: Cytomegalovirus, HHV: Human herpes virus, RMSF: Rocky mountain spotted fever				

rise in hematocrit values reveal substantial plasma loss, mandating quick volume replacement. Changes in urine output and hematocrit values guide the rate of administration of fluids. The hematocrit values in conjunction with the clinical signs (stable pulse rate and blood pressure and increasing urine output), should be used to assess for improvement. It has sometimes been suggested to continue or even increase intravenous fluids until the hematocrit decreases or to achieve a particular number. This puts the patient at risk of fluid overload particularly in the later stages of the illness. Patients with signs of circulatory compromise should immediately receive rapid volume replacement with 10-20 ml/kg/hour of crystalloid solution. If no improvement is noted, oxygen should be administered, and the crystalloid solution should be replaced with colloid (if hematocrit is rising) or blood (if hematocrit falls. Prophylactic platelets may be given at level of <10,000/cumm in the absence of bleeding manifestations. In the case of systemic massive bleeding platelet transfusion may be needed along with red cell transfusion. Liver functions should also be monitored.[14]

Management of dengue shock syndrome

This is a medical emergency, and every minute counts towards a favorable outcome. Without delay, adequate fluid replacement is necessary where there are massive plasma losses. Delayed or inadequate fluid resuscitation can cause multisystem organ dysfunction that may lead to death. Electrolyte (sodium, calcium) and acid-base disturbances may occur and there is a high potential for developing disseminated intravascular coagulopathy in cases with prolonged shock.

Intravenous fluid therapy should be adjusted after close monitoring at 1-2 hourly intervals, throughout the 24 h period. Establishment of central venous pressure may be necessary in the management of severe cases that are not easily reversible. In patients with massive plasma leakage and in whom a large volume of crystalloid has been given Colloidal fluid is indicated. In cases with persistent shock despite a decline in hematocrit after initial fluid replacement and resuscitation with plasma or plasma expanders, internal bleeding should be suspected. Blood transfusions may then be indicated.[14]

Conclusion

It is a challenge to monitor dengue viral infection since it continues to involve newer zones, newer populations and is growing in magnitude and epidemic after epidemic. In conclusion, dengue viral infection presents a broad range of systemic and oral manifestations. As dental professionals, it is also essential to identify the oral presentations of dengue since the oral cavity is a common site of hemorrhage and may be the only early manifestation of the disease.

Right identification induces an early diagnosis, prompt institution of treatment and avoidance of significant complications.

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