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Occurrence of muco-cutaneous lesions in children's diagnosed with dengue fever

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Abstract
Skin lesions may be the presenting feature of dengue fever and can be helpful in the diagnosis of the disease. Hence, a clear understanding of these skin manifestations is required for clinicians to diagnose and treat the condition accordingly. Uptil now few studies are available regarding the spectrum of cutaneous features of dengue infection. The purpose of this study was to observe the pattern and frequency of mucocutaneous manifestations in patients of dengue fever in our hospital.
The study was planned in Upgraded Department of Pediatrics, Patna medical College and Hospital, Patna, Bihar. The study was conducted from the July 2015 to June 2016. The 50 cases diagnosed positive for Dengue fever were evaluated in the present study. A clinical history, physical examination and relevant baseline investigations were done for all the cases. Patients were monitored for development of cutaneous and mucosal manifestations. A pre-structured proforma, which include demographic details of the patient, severity of illness, various mucosal and cutaneous manifestations and day of occurrence of the same, was used to record the clinical data and laboratory parameters from cases selected for the study. The patients were managed according to WHO protocol.
The frequency of dengue fever outbreaks has increased in our country. Early recognition of cutaneous features is important as dengue fever may progress to the life-threatening dengue hemorrhagic fever or dengue shock syndrome. A variety of cutaneous features were observed in patients of dengue viral infection. The commonest was Macular Rash, Pruritus, Petechia, Flushing etc.

Keywords: muco-cutaneous lesions, Dengue fever, Children. etc

Introduction
Dengue fever is a mosquito-borne viral disease caused by one of four antigenically distinct dengue flaviviruses: dengue virus 1 (DEN-1), dengue virus 2 (DEN-2), dengue virus 3 (DEN-3), and dengue virus 4 (DEN-4). The Aedes aegypti mosquito transmits the virus while ingesting a blood meal. Primary viral infection occurs with any of the four serotypes. Dengue hemmorhagic fever (DHF) is a more severe form of dengue fever associated with thrombocytopenia and hemoconcentration. A patient can be infected by at least two, if not all four types (ie, DEN-1, DEN-2, DEN-3, DEN-4), at different times, and the infection can reoccur once during a person's lifetime.
Viral infection may lead to acute illness with fever and 2 or more of the following symptoms: headache, retro-orbital pain, myalgia, arthralgia, rash, and hemorrhagic manifestations. In 2004, dengue fever resulted in a case of permanent bilateral visual loss. The vision complication was a result of retinal capillary occlusion [1]. Fever and other symptoms may subside after 3-4 days, and the patient may recover completely, or the fever may return with a rash within 1-3 days. Dengue, frequently called breakbone fever, is endemic to large areas of the tropics and subtropics, including the Caribbean Islands.
Dengue is a public health concern because most of the population in tropical America is susceptible to infection. A serosurvey conducted after the first confirmed dengue outbreak in Peru in 1990 demonstrated that an earlier outbreak of dengue transmission had been undetected. The silent transmission of dengue was demonstrated in 1992 in an area of Taiwan that was believed to be free of the disease.
Recent outbreaks of dengue in nearby Caribbean, Central American, and South American countries increase the likelihood of future autochthonous transmission among people in Florida and Southeastern states [2]. Cases of dengue fever reported in Texas and Israel occurred from travelers who were infected with dengue while visiting other countries. The risk of autochthonous transmission increased when they returned home.
Dengue fever has become more prevalent because of increased travel into regions where dengue is common. In 2000, 674 million travelers boarded ships and airline for international travel. In 2012, more than one billion people were recorded to have traveled internationally. Dengue fever is a mosquito-borne viral disease caused by 1 of 4 antigenically distinct dengue flaviviruses: DEN-1, DEN-2, DEN-3, and DEN-4.
Dengue is transmitted to humans through the bite of infected A aegypti mosquitoes. Persons with dengue flaviviruses in their blood can transmit the flaviviruses to the mosquito (the vector) 1 day before the onset of the febrile period. The patient can remain infectious for the next 6-7 days. After an A aegypti mosquito ingests the flavivirus from an infected human during a blood meal, the flavivirus replicates for 8-12 days. After the incubation phase, the mosquito remains infectious for life. The flavivirus multiplies in the gut of the mosquito and attains a high titer in its salivary glands.
The mosquito transmits the flavivirus when a fresh human host is bitten. The virus does not adversely affect the mosquito. The life span of A aegypti, the primary vector of

dengue in the Americas, is usually 21 days. The life span of A aegypti and the incubation period depend on the temperature and rainfall in the region. An animal reservoir is not necessary to maintain the cycle of transmission of dengue fever, but an animal reservoir in the form of monkeys appears to exist in limited areas of Africa.

In the continental United States, dengue occurs only in the season when mosquitoes breed actively (warm weather). Since the 1970s, outbreaks of dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) have increased in frequency and severity in the Caribbean and the Americas. In the past 2 years, an increasing number of reports of dengue fever have occurred in the United States, particularly from travelers to areas indigenous to the disease.

A aegypti and Aedes albopictus, a recently introduced vector species, have been found throughout Florida. A aegypti breeds year-round in southern Florida. The last dengue epidemic in Florida (in the Tampa and Miami areas) occurred in 1934-1935 and affected an estimated 15,000 people among the population of 135,000 in Miami. The last recorded epidemic in the southeastern United States occurred in Louisiana in 1945. Outbreaks of dengue also occurred in Laredo, Texas in 1998. Other outbreaks of dengue have occurred in southern Texas multiple times, including in 2004-2005, and in Florida in 2009-2011 and Hawaii [3].

Approximately 40% of the world's population (2.5 billion people) resides in regions in which dengue is endemic, and dengue is endemic in 112 countries in the world. Annually, 100 million cases of dengue fever and 500,000 cases of DHF are reported worldwide. The reported 500,000 cases of DHF in 2004 is a tremendous increase from the 2002 data. This should prompt further concern as to the seriousness of the epidemic. Dengue and other arboviruses (ie, arthropod-borne viruses) have attracted a good deal of attention because of an increasingly mobile population that progressively impinges on jungle terrain.

According to the surveillance data, almost 200,000 cases of dengue fever occur yearly in 31 countries in Central America and South America. The rate among disease-endemic populations may be as high as 6400 cases per 100,000 persons exposed to mosquito bites. Data on the rate of dengue among travelers are scarce. Since the 1970s, outbreaks of dengue fever, DHF, and DSS have increased in frequency and severity in the Caribbean.

People of all ages are affected. Compared with younger individuals, elderly persons are more likely to be at risk because of coexisting medical concerns. Of patients with DHF, 90% are younger than 15 years.

With early diagnosis and supportive care, fatalities are rare. Convalescence is slow. Aspirin and NSAIDs are discouraged owing to potential platelet dysfunction causing bleeding. Children who receive aspirin are at risk of developing Reyes syndrome; therefore, they should never receive aspirin when Dengue fever is suspected. The mortality rate of DSS is reported to be 2%. Exposure to a serotype besides the 4 mentioned can lead to DHF or DSS, which have serious complications and may be fatal. DSS can occur after DHF, with symptoms of circulatory and respiratory failure that may result in death. Rare complications include depression, pneumonia, iritis, orchitis, and oophoritis. Secondary reinfection is unlikely because of preexisting antibodies.

No fetal malformations were seen in any of the babies born in one study. The single patient who developed DHF in the first trimester had an abortion while having acute symptoms of dengue. Three cases of maternal death due to dengue fever in the third trimester have been reported. An awareness of the clinical and laboratory manifestations of dengue in pregnancy should allow its early recognition and the institution of appropriate treatment [4, 5].

Patients have a history of recent travel to a region where dengue is endemic. Symptoms begin with a sudden onset of high fever (temperature >101°F), chills, and a severe (termed breakbone) aching of the head, back, and extremities. DHF begins with a sudden elevation in temperature as seen in dengue fever. Of patients with DHF, 90% are younger than 15 years. Current studies show that T cells that are reactive to the dengue fever virus may be contributors to the development of DHF. The fever persists for 2-7 days and defervescence is followed by the development of hemorrhagic symptoms such as bleeding from sites of trauma, gastrointestinal bleeding, and hematuria. Patients may also present with abdominal pain, vomiting, febrile seizures (in children), and a decreased level of consciousness. Diarrhea rarely is a symptom in patients with dengue fever.

Sore throat, prostration, and depression are accompanied by conjunctival redness and flushing or blotching of the skin. The initial febrile phase lasts 3-4 days followed by a remission of a few hours to a few days. Skin eruptions appear in 80% of patients during the remission of the fever. Approximately one half of patients develop a centrifugal macular, maculopapular, scarlatiniform, or petechial eruption [2, 6, 7]. The cutaneous eruptions may become confluent, with small, round islands of sparing, the so-called white islands in a sea of red [8]. The rash characteristically starts on the dorsum of the hands and feet and spreads to the arms, legs, and torso; the face is rarely involved. The eruption seen in dengue lasts 2 hours to several days. Before it appears, distinguishing dengue from malaria, yellow fever, or influenza is difficult.

Serum samples obtained during the acute stage and during convalescence should be sent to the laboratory for immunoglobulin M antibody–capture enzyme-linked immunosorbent assay (MAC-ELISA). MAC-ELISA is used for disease monitoring. Positive results should be reported to public health authorities.

Medical care is entirely symptomatic. Symptomatic treatment is usually effective. The death rate for untreated DHF/DSS can be as high as 10-15% in places where emergency supportive treatment with intravenous fluids and platelet replacement is not readily accessible.

Analgesics, fluid replacement, and bed rest are usually sufficient. Permit the patient to gradually resume their previous activities, especially during the long period of convalescence. Local and state health authorities should be alerted about new cases of dengue fever. Alert health care providers about the occurrence. Outbreaks of dengue will increasingly cross common borders of endemic and disease-free countries unless (1) health surveillance is increased, (2) new cases are promptly reported, (3) professional awareness is heightened, and (4) public education is provided.

Encourage participation in mosquito-abatement activities. Examples include insecticide fogging, the elimination of mosquito-breeding sites, the disposal of refuse and old tires, covering water receptacles, and changing water in birdbaths daily. Encourage patients to use personal protection such as skin repellants and mosquito screens and advise them to avoid mosquito-breeding sites.

An experimental vaccine is being developed. New vaccines

for different dengue serotypes are available, but they are difficult to obtain. Recombinant DNA technology has contributed to the potential development of novel live-attenuated vaccines against dengue viruses [9]; however, because of adaptability and a short generation time of dengue viruses, developing an effective vaccine will continue to be a challenge. Genomic mapping of the mosquito vector, A aegypti, can help advance viral containment efforts [10, 11]. Scientists supported by research in the National Institute of Allergy and Infectious Disease (NIAID) are developing weakened versions of dengue virus for a potential vaccine. New, ongoing research by the NIAID is shedding light on how the dengue virus interacts with damaged cells [12, 13].

Skin lesions may be the presenting feature of dengue fever and can be helpful in the diagnosis of the disease. Hence, a clear understanding of these skin manifestations is required for clinicians to diagnose and treat the condition accordingly. Uptil now few studies are available regarding the spectrum of cutaneous features of dengue infection. The purpose of this study was to observe the pattern and frequency of mucocutaneous manifestations in patients of dengue fever in our hospital.

Methodology

The study was planned in Upgraded Department of Pediatrics, Patna medical College and Hospital, Patna, Bihar. The study was conducted from the July 2015 to June 2016. The 50 cases diagnosed positive for Dengue fever were evaluated in the present study.

A clinical history, physical examination and relevant baseline investigations were done for all the cases. Patients were monitored for development of cutaneous and mucosal manifestations. A pre-structured proforma, which include demographic details of the patient, severity of illness, various mucosal and cutaneous manifestations and day of occurrence of the same, was used to record the clinical data and laboratory parameters from cases selected for the study. The patients were managed according to WHO protocol.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Children with age less than 18 years, admitted as Dengue; fever based on clinical features as described in WHO 2012 Guidelines and positive Ns1Ag and/or Dengue IgM.

Exclusion Criteria: Children who cannot be followed up till 7 days; Mucocutaneous changes due to drugs or blood transfusion; Children with pre-existing diseases on Chronic medications; Children with pre-existing skin diseases; Children with dengue fever associated with other illnesses. example: chikungunya, malaria, typhoid, etc.

Results & Discussion

There are a very few studies on mucocutaneous manifestations of dengue fever, but not a single published study exclusively in children. Mucocutaneous manifestations are commonly seen in Dengue fever. Dengue fever is a rapidly growing public health problem especially of the tropical and subtropical countries. Estimates have suggested that 50 to 100 million cases of dengue occur annually [15, 17].

The spectrum of dengue varies from asymptomatic infection to death. Cutaneous findings are prominently seen in patients of dengue fever and have been reported to occur in 80% of patients.16 According to a study conducted by Thomas *et al*, in which 124 cases of dengue viral illness were studied; skin manifestations were seen in 46.8% patients [14].

It is evident that the threat from the dengue fever is large and growing. The past 6 decades have witnessed a worrisome rise in epidemics as well as an increase in disease severity [18]. It might be due to changing climate, urbanisation, poor living conditions, and inadequate waste disposal. The striking features of DF are fever, headache, flushed faces, conjuctival injection, lymphadenopathy, backache, severe malaise, muscle and bone pains, nausea, vomiting and mild sore throat [19]. There are several significant dermatological features of DF, DHF and DSS. Dengue fever commonly presents with specific skin lesions. The skin lesions can be a clue to the diagnosis in difficult cases.12

More than 50% of infected patients report having a rash during the febrile period.8 This rash is considered to be due to interaction of the virus with the host cells causing release of different chemical mediators and initiation of immunological mechanisms. Histopathology has revealed changes in the endothelium of blood vessels, perivascular edema, as well as, infiltration of mononuclear cells, while no change occurs in the epidermis, dermis or subcutaneous tissue [20].

Table 1: Serology Results

Serology Results	No. of Cases
Dengue Positive	50
Dengue Negative	353
Total	403

Table 2: Dengue Fever with and Without Mucocutaneous Manifestations

Mucocutaneous manifestations	No. of Cases
Positive	34
Negative	14
Total	50

Table 3: Muco-Cutaneous Manifestations

Cutaneous Manifestations	No of Cases
Macular Rash	23
Papular Rash	7
Pruritus	22
Morbilliform Rash	7
Ecchymosis	3
Desquamation	3
Petechia	21
Flushing	47

Table 4: Different Types of Mucosal Manifestations

Mucosal Manifestations	No of Cases
Oral (Vesicles on Soft Palate) Throat Congestion	15
Erythema and Crusting of Lips and Tongue	16
Scleral Congestions/ Conjuctival Haemorrhage	24
Nasal/Palatal Haem orrhage/gingival bleeding	6

Table 5: Mucosal Manifestations with Day of Occurrence

Mucosal Manifestation	Occurrence in Days	Mode in Days
Vesicles on Soft Palate/Throat congestion	3-4	3
Erythema and Crusting of Lips and Tongue	3-4	4
Scleral Congestion/Conjunctival Haemorrhage	2-5	3
Nasal or Palatal Haemorrhage / Gingival Bleeding	4-5	4

Study by Thomas EA *et al* found haemorrhagic manifestations on the skin such as petechiae, purpura, or ecchymosis with positive tourniquet test, more commonly in DHF and DSS than in DF and also mucosal involvement more commonly in patients with DHF than with DF [21]. The spectrum of dengue varies from asymptomatic infection to death. Cutaneous findings are prominently seen in patients of dengue fever.

Severe dengue is life-threatening from bleeding (dengue hemorrhagic fever), Dengue shock syndrome, or severe organ impairment (hepatic, renal, cardiac, pulmonary, and brain). The bleeding results from microangiopathy, while platelet number is insufficient to block the bleeding points. Shock results from capillary plasma leakage from vascular to extracellular spaces. Organ failure is presumably due to microangiopathy resulting in impaired perfusion. While dengue fever is relatively inconsequential, severe dengue has a significant fatality rate [22]. The World Health Organization criteria exist for the classification of dengue into three clinical categories. Infection with DENV causes three clinical syndromes with undifferentiated viral syndrome, classic dengue fever, dengue hemorrhagic fever, and Dengue shock syndrome. However, there is a significant overlap between these three categories [23].

The limitations of the study were lack of data on the disease onset; the pattern, types and extent of skin lesions; presence of mucosal lesions, details of progression or regression of lesions, details of associated pruritus, presence of hand and leg oedema, availability of DNA RT-PCR, details of dengue virus serotype, and cutaneous biopsy. Availability of these would make the description of skin lesion more robust, however, it might not change the outcome that has been interpreted in the study. The study did not included children with dengue, in whom the complications of the infection are known to be higher [24].

Conclusion

The frequency of dengue fever outbreaks has increased in our country. Early recognition of cutaneous features is important as dengue fever may progress to the life-threatening dengue hemorrhagic fever or dengue shock syndrome. A variety of cutaneous features were observed in patients of dengue viral infection. The commonest was Macular Rash, Pruritus, Petechia., Flushing etc.

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