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Dengue: A Serious Global Health Problem

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Abstract

In the recent years, dengue incidences have been reported from every corner of the world. Dengue is a viral disease which gets transmitted to humans, due to the biting of infected Aedes mosquitoes, mainly Aedes aegypti. This article aims to provide information on the various aspects of dengue. Bibliographic investigation was done to retrieve available published literature by scrutinizing peer reviewed papers, accessing worldwide accepted scientific databases (Scopus, PubMed, SciELO, NISCAIR, Google Scholar and WHO Guidelines available during 1994-2016). Overall, 100 articles were reviewed properly, and out of the reviewed literature, only 22 articles from year 1994-2016 were selected for the study. This article gives the details of dengue criteria, transmission, methods of laboratory diagnosis, clinical management (including stepwise approach to the dengue management) and vector management (including biological control). Recently launched Caripill tablets and Dengvaxia vaccine are the main findings of this study. Caripill tablet has been claimed to increase the platelet count, a major milestone achieved. This article will show a path to the healthcare professionals, including clinicians. It will also create public awareness regarding dengue. There is a huge scope to carry out further research on dengue.

Keywords: Dengue; Aedes aegypti; Platelet count; Caripil; Dengvaxia

Abbreviations

ALT: Alanine Transaminase; AST: Aspartate Transaminase; AYUSH: Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy; CNS: Central Nervous System; ECG: Electrocardiogram; Ig: Immunoglobulin; I.V.: Intravenous; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; RNA: Ribonucleic Acid; WBC: White Blood Cell; WHO: World Health Organization.

Introduction

Dengue is a viral disease which gets transmitted to humans, due to the biting of infected *Aedes* mosquitoes, mainly *Aedes aegypti*. Dengue incidence has multiplied by 30-fold in the last 50 years. Dengue incidence has been reported in new countries also, where it was not found. Approximately 50 million new cases are reported every year. And, near about 2.5 billion people are living in those countries, which are endemic to dengue [1].

Dengue Criteria

Probable dengue

Person either lives in or travels to areas which are endemic to dengue. Any two criteria along with fever should be present: rash, nausea, vomiting, tourniquet test positive, aches and pains, leukopenia, any warning sign (like persistent vomiting, abdominal pain or tenderness, mucosal bleed, clinical fluid accumulation, liver enlargement >2 cm, lethargy, restlessness, increase in hematocrit concurrent with rapid decrease in platelet count).

Severe Dengue

- If there is excessive leakage of plasma causing fluid accumulation, respiratory distress or shock.
- If there is excessive bleeding, examined by clinician.
- If there is severe involvement of organs, like CNS (altered consciousness), liver (ALT/AST ≥ 1000 U/L), other organs including heart.

Transmission

The virus

Dengue virus comes under the genus Flavivirus and family Flavivirid *Aedes*. It is a small RNA virus (single-stranded). Four distinct serotypes of dengue virus occur, namely DEN 1 to 4 [2-4].

The Vectors

Dengue virus gets transmitted to humans, due to the biting of infected *Aedes* mosquitoes, mainly *Aedes aegypti*. This mosquito is found mainly in tropical and subtropical areas of the world, under latitudes 350N and 350S. These areas correspond to a winter isotherm of 100C (approximately).

The immature stages of *Aedes* mosquitoes are found in water-filled habitats, mainly in artificial containers. These containers are closely associated with residential areas of humans. Most of the female *Aedes aegypti* spend their life nearby the houses where they finally grow as adults. This proves that people, and not mosquitoes, move the virus among different human communities.

Several species of *Aedes* mosquitoes have been found to be responsible for the Dengue outbreaks, e.g. *Aedes* albopictus, *Aedes polynesiensis*, *Aedes scutellaris*. These species have different behavior, ecology and geographical distribution.

The host

In human beings, incubation period is of 4-10 days. Most of the infections are asymptomatic, but a wide range of clinical manifestations can be produced by the different serotypes of *Aedes* mosquitoes. It is supposed that primary infection provides lifelong immunity to that particular serotype and a temporary protection to different serotypes for a maximum duration of 2-3 months [5].

Risk factors for dengue include age, ethnicity, secondary infection and chronic diseases like sickle cell anaemia, bronchial asthma and diabetes mellitus. Children are more prone to dengue shock, because they are less capable to compensate for capillary leakage as compared to adults.

When an infected mosquito will take blood, then the dengue virus will enter the human body via the skin. Virus is present in the blood during the acute phase of infection. Virus clearance is done mainly by humoral and cellular immune systems. These systems generate neutralizing antibodies and activate CD4+ and CD8+ T lymphocytes, which cause virus clearance.

Abnormalities in homeostasis, haemoconcentration and plasma leakage are the characteristics features of severe dengue. Genetic constitution of the individual, the immune response and the virus characteristics are risk factors for severe dengue.

Recent studies say that plasma leakage is mediated by the activation of endothelial cell. Changes in megakaryocytopoieses causes thrombocytopenia, which leads to platelet dysfunction, increased consumption or destruction. These processes will ultimately cause haemorrhage [6,7].

Dengue virus transmission

The main host for dengue virus is humans. Female mosquitoes ingest the dengue virus, which is moving in the infected humans. This virus then infects the mid-gut of mosquito. After that, it spreads through systemic circulation, in a time span of 8–12 days. This is known as extrinsic incubation period. Thereafter, this virus gets transmitted to other humans during successive feeding. Environmental conditions (e.g. room temperature) affect the extrinsic incubation period. After this, the mosquito remains infective throughout its life. *Aedes aegypti* is the main vector for this virus. Reasons are it lives in nearby areas of humans, its anthrophilic nature and it bites many times before oogenesis gets completed.

Factors affecting the transmission of virus are: immunological factors of the population, climate and environmental factors and interactions between host-pathogen. Climate directly affects the biology of the vectors. So, climate affects the distribution and abundance of the vectors and it is the main factor responsible for dengue epidemics.

Material and Methods

Bibliographic investigation was done to retrieve available published literature by scrutinizing peer reviewed papers, accessing worldwide accepted scientific databases (Scopus, PubMed, SciELO, NISCAIR, Google Scholar and WHO Guidelines available during 1994-2016). Overall, 100 articles were

reviewed properly, and out of the reviewed literature, only 23 articles from year 1994-2016 were selected for the study.

Results and Discussion

Methods of laboratory diagnosis

Correct diagnosis of dengue is of utmost value for clinical care, pathogenesis, control of outbreak, activities related with surveillance, academic research, development of vaccine and clinical trials.

Methods of laboratory diagnosis to confirm infection of dengue virus, involve detection of the virus, viral nucleic acid, antigens or antibodies. Serology is the preferred method for diagnosis after the completion of acute phase of infection. But, for the early stages of illness, the preferred method for diagnosis is isolation of virus, detection of nucleic acid or antigen.

Immune status of the host determines the antibody response to infection [8].

If dengue infects a person who has not been previously infected by a dengue virus, then the first immunoglobulin to appear is IgM. During days 3-5 of illness, IgM can be detected in 50% of patients; then by day 5, it rises to 80% and then by day 10, it rises to 99%. Peak levels of IgM antibodies are achieved after two weeks of onset of illness and then it declines to untraceable level after 2-3 months. After the first week of illness, IgG antibodies come to a detectable range, then it increases slowly and IgG antibodies are detectable even after several months, and even for whole life [9-11].

If dengue infects a person who has been previously infected by a dengue virus, then IgG is the dominant immunoglobulin. IgM levels are very low in secondary infections as compared to primary ones. Ratio of IgM/IgG is more commonly used to distinguish primary and secondary dengue infections, as compared to haemagglutination-inhibition test (HI) [12-14].

Factors that are taken into account while choosing appropriate laboratory diagnostic methods are: purpose of the testing, availability of laboratory facilities and technical expertise, time of sample collection and cost.

Generally, complex technologies and technical expertise are used for the tests with high sensitivity and specificity. Whereas, sensitivity and specificity is compromised in rapid tests for fast result. Isolation of virus and detection of nucleic acid are more specific but also more labor-intensive and costly as compared to serological methods for the detection of antibodies.

Clinical Management

Dengue infection is a dynamic disease affecting systemically. Clinical presentation is very broad including clinical manifestations of severe and non-severe nature. The illness begins abruptly after the incubation period. There are three phases of the illness febrile, critical and recovery.

Even though, manifestations of dengue disease is complex, its management is inexpensive, not complex and capable to save lives. But for that, correct intervention should be given at the right time. Early identification and understanding of the disease, leads to a systematic management of the case and that gives a good clinical outcome.

Patients are first seen, examined and evaluated at the primary and secondary care levels. Management decisions at this level are important in concluding the clinical outcome. A good response decreases the hospitalization and save the patient's life. Dengue cases examined in primary and secondary care should be notified early. This will help in identification of outbreaks, so that an early response can be initiated. Summary of problems occurring in different phases of dengue, are given in Table 1.

Table 1: Different phases of dengue.

S. No	Name of Phase	Characteristics
1	Febrile phase	High fever, febrile seizures and dehydration
2	Critical phase	Shock due to organ impairment, plasma leakage and severe haemorrhage
3	Recovery phase	Hypervolemia due to excessive i.v. fluid therapy

Severe Dengue

A patient is known to suffer from severe dengue, if he/she belongs to a dengue risk area along with fever of 2–7 days as well as he/she should have any of the features: evidence of leakage of plasma (like haematocrit value is high, ascites or pleural effusions, shock or circulatory compromise), significant bleeding, impaired consciousness, severe involvement of gastrointestinal tract (regular vomiting, excessive abdominal pain, jaundice), severe impairment of organs (acute renal failure, acute liver failure, encephalopathy, cardiomyopathy), other unusual manifestations.

Case Management

Early identification of the disease, its management and referral (if required) can reduce mortality due to the dengue. This requires the delivery of good clinical services from primary to tertiary levels of health care.

Majority of the patients suffering from dengue become alright without hospitalization. But, some of them develop severe form of the disease. Severe cases can be identified at the primary and secondary care levels by the application of management decisions and effective triage principles. Severe cases require hospitalization in referral centres, where all the necessary management should be given [15].

Stepwise Approach to the Dengue Management

First step - Overall assessment

Complete history

It includes: when the fever/illness started, how much quantity he/she is taking orally, analysis of warning signs, diarrhea, altered mental state/ dizziness /seizure, what is the urine output (volume, frequency and last voiding), other histories (like co-existing conditions, travel to areas where dengue has spreaded, family or neighborhood dengue, swimming in waterfall, jungle trekking and recent unprotected sex or drug abuse).

Physical examination

It includes: examination of mental well-being, examination of hydration, examination of haemodynamics, examination for pleural effusion/ tachypnea, examination for ascites/ tenderness, examination for bleeding and rash, tourniquet test

Investigation

It includes: full blood count, hematocrit test, WBC count (decreasing), platelet count (rapidly decreasing).

Diagnosis is confirmed by the laboratory tests. Additional tests are tests of glucose, urea, creatinine, liver function, lactate, bicarbonate, serum electrolytes, cardiac enzymes, ECG and specific gravity of urine.

Second step - Diagnosis, assessment of phase of the disease and severity

Clinicians diagnose the given case as dengue, after having complete history, physical examination, haematocrit and full blood count. Clinicians also determine the phase of dengue (febrile, critical or recovery), haemodynamics, warning signs and hydration of the patient. Hospitalization of the patient is also determined by the clinicians.

Third step – Management

Notification of the disease

Suitable public health interventions can be initiated in dengue-endemic countries, if cases of suspected, probable and confirmed dengue are brought to notice at the earliest. Confirmation with laboratory investigation is not mandatory before notification, but it should be taken. Confirmed cases are only notified in non-endemic countries.

Criteria for suspected cases are: patient has travelled to a dengue-endemic area or patient lives in a dengue-endemic area, has decreasing white cell counts, has fever for three days or more, and/or has thrombocytopenia ± positive tourniquet test.

It is difficult to prevent the transmission of dengue in dengue-endemic countries, if the notification of the cases is done later.

Management decisions

Patients are categorized into three groups (on the basis of clinical manifestations):

- Group A (Patients who are sent back to home),
- Group B (Patients who require hospitalization),
- Group C (Patients who need emergency treatment and referral) [16].

Treatment for Group A – Patients who are sent back to home

This group includes those patients who are not having any of the warning signs. These patients can tolerate sufficient quantity of oral fluids and can void urine for at least one time in every six hours.

Patients who are not bedridden should be reviewed daily till they are free from the critical stage. Parameters reviewed are WBC count, abatement of fever and warning signs. Patients with stable haematocrit value are sent back to home. But they are instructed to visit the hospital, if they suffer from any of the warning signs.

They are instructed to follow these action plans:

• Intake of ORS, juice of fruits and fluids having sugar and electrolytes should be encouraged, to replenish the losses from vomiting and fever. Sufficient intake of oral fluid decreases hospitalizations [17].

• Paracetamol should be given for high fever. Its dosing interval should not be less than six hours. Lukewarm sponge should be given for persistent high fever.

Aspirin, Ibuprofen and other NSAIDs should be avoided because these drugs increase bleeding or gastritis. Aspirin can also cause Reye's syndrome.

• Patient should visit the hospital immediately, if: there is no improvement clinically, patient's condition worsens at the time of debatement of fever, continuous vomiting, abdominal pain (severe), extremities are cold and clammy, bleeding occurs, urine is not voided for more than 4–6 hours, irritability or restlessness or lethargies.

Daily monitoring of patients (who are sent back to home) should be done. Monitoring parameters include: output of urine (frequency and volume), pattern of temperature, quantity of fluid intake and losses, warning signs, haematocrit value, WBC count, platelet count and signs of bleeding and leakage of plasma.

Treatment for Group B – Patients who require hospitalization

Patients of critical phase require hospitalization for close monitoring. This group includes patients with warning signs, patients with co-existing conditions and patients with social circumstances like living alone.

Action plan for patients having dengue along with warning signs, are as follows:

• Haematocrit should be determined before starting the fluid therapy. Isotonic solutions (like normal saline, Ringer's lactate) should only be given. These solutions should be given at the rate of 5–7 ml/ kg/hour for 1–2 hours, then depending upon the clinical response, it should be reduced to 3–5 ml/kg/hour for 2–4 hours, and then it should be reduced to 2–3 ml/kg/hour or less.

• Clinical status should be reassessed and the haematocrit should be repeated. If the haematocrit is same or rises slightly, then same rate 2–3 ml/kg/hour for next 2–4 hours should be given. If the haematocrit is increasing very fastly and the conditions of vital signs are deteriorating, then increase the rate to 5–10 ml/kg/hour for next 1–2 hours. Again, clinical status should be reassessed, haematocrit should be repeated and fluid infusion rates should be reviewed accordingly.

• Minimum quantity of I.V. fluid should be given to keep optimum perfusion and output of urine should be around 0.5 ml/kg/hour. I.V. fluids are generally required only for 24–48 hours. I.V. fluids should be successively reduced, if the rate of leakage of plasma decreases.

Action plan for patients having dengue without warning signs, are as follows:

• Intake of oral fluids should be appreciated. If oral intake is not tolerated, then I.V. fluid therapy of normal saline should be initiated. Fluid infusion should be revised frequently because patients can take oral fluids after some time of I.V. fluid therapy. Minimum volume should be given to optimize the perfusion and output of urine. I.V. fluids are generally required only for 24–48 hours.

• Monitoring parameters include: output of urine (frequency and volume), pattern of temperature, quantity of fluid intake and losses, warning signs, haematocrit value, WBC count and platelet count.

Treatment for Group C - Patients who need emergency treatment and referral

If the patient is in a critical condition and has: severe leakage of plasma, hemorrhages of severe nature, severe impairment of organs like cardiomyopathy, renal impairment, encephalopathy or encephalitis, hepatic damage.

Then, patients need emergency treatment and referral.

Patients with severe dengue should be hospitalized to a tertiary healthcare center having the facilities of blood transfusion and intensive care. Main intervention required is the i.v. fluid therapy. Haematocrit levels should be obtained before and after i.v. fluid therapy. Isotonic crystalloid solution is used to replenish plasma losses. But colloid solutions are used in the case of hypotensive shock.

Further plasma losses should be continuously replaced to optimize effective circulation for 24–48 hours. Ideal body weight is generally used to calculate fluid infusion rates in the case of obese or overweight patients. For shock patients, cross match is generally done. In the case of severe bleeding only, transfusion of blood should be done.

Fluid resuscitation is entirely different from fluid administration. Fluid resuscitation is a process in which 10–20 ml boluses of fluids are given for a short duration. Response of patient is evaluated to prevent the formation of edema in the lungs.

Aims of fluid resuscitation are to improve circulation (central and peripheral) and to improve perfusion of end-organs – i.e. stability of consciousness, output of urine ≥0.5 ml/kg/hour, metabolic acidosis should decrease.

Vector Management

Prevention of transmission of dengue virus is solely dependent on interruption of human–vector contact or control of the mosquito vectors.

Since *Aedes aegypti* is the main vector, so activities to control transmission should target its habitat, which is in the household and close proximity. Other places like schools, hospitals and workplaces (where human–vector contact occurs), should also be targeted. *Aedes aegypti* grows in household containers where water is purposely filled like domestic water storage and for decorative plants. It also grows near habitats filled with rainwater. Generally, these mosquitoes cannot fly very far away, and most of them remain in an area of 100 metres from where they have been produced. These mosquitoes are totally dependent on humans for feeding, mostly in daytime, and both outdoors as well as indoors.

WHO has developed integrated vector management, which is the systematic approach to control the vectors of dengue [18].

Aedes aegypti is mainly controlled by eliminating container habitats, where they lay their eggs and aquatic stages develop. Various methods of vector control are: management or elimination of larval habitats, use of insecticides for larviciding, biological agents and the application of adulticides.

Points to be noted before choosing the most suitable method for vector control, are: behaviour and local ecology of the target species, availability of resources for implementation, feasibility of methods, cultural background of the area, and the adequacy of coverage.

Biological control

It includes application of organisms that decrease populations of the target species, either by preying upon, parasitizing, or competing with the target species. Certain species of predatory copepods and larvivorous fish are efficient in controlling *Aedes* mosquitoes in specific container habitats. These species are very less used on a large scale.

The main benefit of using biological control is that it prevents environment from getting contaminated by the use of chemicals. Limitations of this method are: cost and tedious work of growing the organisms on a big level, difficulty in their application and their narrow use in water medium. These methods can destroy the immature stages of *Aedes* mosquitoes.

Since, the organisms used in the biological control cannot tolerate dried conditions, so their use is mainly confined to container habitats. Consent of local residents for the application of organisms into water containers is important for the purpose of their distribution and monitoring [19].

Carica Papaya Leaf Extract

Carica papaya leaf extract can be used along with the routine clinical management for dengue. This extract can be given at any stage, but if given from the day 1 of the illness, it will show the maximum effect. This extract can be taken as syrup. Recommended dose is 30 ml thrice daily before food for an adult and for children it is 5-10 ml thrice daily, until the disease is recovered fully. Patients are advised not to leave the therapy in between. To mask the bitter taste of the extract, cold water should be consumed after drinking the extract. If the patient is allergic to papaya, then this extract should be avoided.

Caripill

Recently, Micro Labs, Bengaluru, has launched Caripill tablet in Indian market in 2015, which is claimed to increase the platelet count in dengue. Caripill is an herbal medicine prepared by using Carica papaya leaf extract and has got the approval from the department of AYUSH, Government of India.

Before Caripill tablet, there was no specific tablet for dengue, except paracetamol tablets (650 mg) to subside the fever. But, as the fever used to subside, the platelet count used to decrease resulting in severe ill effects. So, Caripill tablet is the first drug which is supported by adequate scientific data (a multicentic clinical trial was conducted by the lab on 300 patients) to increase the platelet count in dengue. Results of clinical trial has shown that Caripill tablet causes an effective decrease in haemorrhagic condition. Also, the patient does not require blood transfusion like earlier dengue cases to compensate the platelet loss.

The cost of Caripill tablet in India is only Rs 25 per tablet and it is available in all leading pharmacies. Recommended dose is 1 tablet (1100 mg) thrice daily, for five days. So, total cost of Caripill therapy is just Rs 375, which reduces the financial burden of the dengue patient and overcomes their emotional stress [20].

Dengvaxia: World's First Dengue Vaccine

As per the announcements made by Sanofi Pasteur (vaccine division of Sanofi), on 9th December 2015, Mexican authorities have given the permission to market Dengvaxia, the first vaccine to be licensed in the world for the prevention of dengue.

The COFEPRIS (Federal Commission for the Protection against Sanitary Risks) has approved Dengvaxia (tetravalent dengue vaccine), for dengue prevention caused by all four serotypes, in the age group of 9 to 45 years residing in dengue endemic areas [21].

Approval of Dengvaxia is based on the clinical trial including more than 40,000 people of various ages, ethnic and socio-economic backgrounds and geographic and epidemiological settings, residing in 15 countries. People from dengue hit areas of Mexico have taken part in this trial for the vaccine development [22].

Conclusion

This review gives a comprehensive knowledge of dengue, about its transmission, methods of laboratory diagnosis, clinical management and vector control. It will be interesting to observe the effects of newly launched Caripill tablets and Dengvaxia vaccine over dengue patients. Public awareness regarding vector control is the need of the hour. Further research should be carried out to develop new medicines, herbal formulations and vaccine to combat this disease in a more efficient way.

Conflicts of Interests

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