Dengue

Subjects: Pathology
Contributor: Kranthi Swaroop Koonisetty

Dengue fever is one of the most important viral infections transmitted by Aedes mosquitoes and a major cause of morbidity and mortality globally.

Keywords: Aedes ; dengue ; global ; KAP ; morbidity ; physicians ; treatment

1. Introduction

Dengue fever is a mosquito-borne viral disease that is spreading at a rapid rate across the globe, with an estimated 390 million dengue infections per year [1][2]. Dengue virus is transmitted via the bite of an infected female *Aedes* mosquito [3][4]. The four main dengue virus (DENV) serotypes responsible for causing the infection are DENV-1, DENV-2, DENV-3, and DENV-4 [5]. The infection is primarily characterized by fever, nausea, rash, vomiting, and aches or pains typically behind the eyes, muscles, joints, or bones [6][7]. These symptoms usually last for 2–7 days [1][3][7]. Sometimes, the infection becomes severe and causes internal bleeding, resulting in dengue hemorrhagic fever (dengue with a warning sign). In more serious conditions, it may lead to the development of dengue shock syndrome or even death [8].

Dengue fever is predominantly seen in tropical and subtropical regions. Asian countries represent 70 percent of the global disease burden of dengue fever [1][2]. In India, dengue fever is endemic in almost all the states and is the leading cause of hospitalization [9]. Many decades earlier, it had a predominant urban distribution but is now reported in rural areas as well [9]. Dengue fever has been a major public health concern in Bangladesh since 2000 [10]. During the 2000 outbreak, DENV-3 was the predominant serotype [11]. After 2000, there has been an outbreak every year with different severity and amplitude [10]. The first major dengue fever outbreak in Malaysia was recorded in 1973 [12]. An increase in dengue cases was seen between 1980–2000 due to rapid population and infrastructure growth [13]. In the 21st century, a seven-fold increase was seen in cases from 2000–2010 [13]. Turkey is not considered a dengue-endemic country anymore because the last severe dengue fever outbreak in Turkey was reported in the late 1920s [14]. This outbreak has infected more than 1 million and caused the death of nearly 1500 people [14]. However, the existence of *Ae. albopictus* was first recorded in Turkey (Edirne) in 2011 [15]. Recently in 2015, the reoccurrence of *Ae. aegypti* and wide distribution of *Ae. albopictus* populations were reported in the Black Sea region [16]. Reasons for the rapid transmission of dengue fever in these countries include (1) temperature and climatic conditions that play a key role in viral replication, infective periods, and viral-vector survival [17][18][19]; (2) globalization, international travel, and trade that increases the risk of epidemic transmission [20]; and (3) increasing population, socioeconomic and behavioral factors, such as not using insect repellents, water storage, and disposal techniques, poor sanitation, and low income, in the countries located in the tropical and subtropical regions [19][21].

After the onset of dengue fever, the virus can be isolated and detected in the circulating blood cells, serum, and plasma within 4–5 days [22]. Antibodies against the dengue virus are detectable in 99 percent of the patients within 10 days of disease onset, with serologic tests [22]. Nonetheless, an array of laboratory diagnostic methods are available for detecting dengue fever. The choice of the diagnostic method depends on the patient's signs and symptoms, time of sample collection, costs, and available laboratory facilities [23]. There is no effective vaccine for dengue fever. Instead, it is usually managed based on the clinical signs and symptoms of the infected patients [24]. Basic steps of dengue management include (1) treating the early febrile phase of dengue fever with the WHO recommended nonsteroidal anti-inflammatory agents (NSAIDs); (2) initiating oral or intravenous fluid therapy to stabilize hemodynamic status, transfusing blood in the case of severe bleeding; and (3) closely monitoring other clinical parameters, such as platelet count, hematocrit, and urine output [22].

2. Current status of dengue fever treatment

The key to favorable clinical outcomes in dengue fever is early detection and effective management of symptoms by health care professionals (HCPs) [6][25]. Thus, the knowledge of HCPs plays a vital role in the diagnosis and management

of dengue fever, thereby reducing its complications, morbidity, and mortality rates. A few studies conducted to assess the knowledge, attitudes, and practices (KAP) of HCPs in the management of dengue fever showed good knowledge among physicians regarding dengue fever [26][27][28]. Another KAP study showed that only a moderate level of knowledge was observed in 49 percent of the HCPs, with room for improvement in their level of attitude and practice concerning dengue fever (dengue without warning sign) prevention [29]. One study reported that almost every physician in the sample knew that aspirin and non-steroidal anti-inflammatory drugs must be avoided during dengue fever or shock syndrome (severe dengue) [30]. However, other studies reported that physicians lacked knowledge about clinical signs, symptoms, and treatment for dengue patients [31]. One published study anticipated there were significant variations in clinical practice by physician's age group and practice setting [27]. At the same time, other published studies reported that the KAP of healthcare professionals for dengue fever was not well established [29][30][32]. To our best knowledge, there were no KAP studies conducted among physicians in India, Bangladesh, Malaysia, and Turkey.

Due to the rapid geographic expansion of *Aedes* mosquitoes [33][34][35][36], it is important to have proper knowledge and practices among physicians for dengue fever diagnosis and treatment. Several studies conducted in developing countries revealed that the diagnostic facilities for dengue fever were poor, especially in the rural regions [7][37][38]. Because of this, physicians need to have better knowledge and understanding of dengue fever for early detection and management. The assessment of physicians' KAP level plays a significant role in dengue diagnosis and treatment. Previous studies that assessed the KAP levels of physicians were based on a small geographic area [28][32].

Irrespective of their country of practice, many physicians failed to identify the scenario for initiation of IV fluid therapy and the reasons for NSAIDs and corticosteroid contraindication in dengue fever. Fair knowledge on these topics is vital for effectively managing dengue fever and preventing complications associated with it. In addition, the majority of physicians failed to identify the parameters of incomplete blood count that helps to determine plasma leakage.

The mean KAP score of the physicians in Turkey was found to be 11.7, whereas, for those practicing in Bangladesh, India, and Malaysia, it was found to be 16.9, 18.03, and 18.46, respectively. The relatively low score which was observed among the physicians from Turkey could be because there are no active dengue cases in Turkey [14]. In addition, Aedes aegypti was reported in the Turkish Mosquito Fauna Checklist in 1959, but it was confirmed that it was not found anymore in 2001 [39]. However, recent arboviral screening in northeastern Turkey revealed a territorial expansion of Aedes species, which is alarming [40]. Therefore, continuous medical training on dengue fever management and sound clinical knowledge is still essential among the physicians practicing in Turkey.

Despite the lack of evidence, the practice of prophylactic platelet transfusion is reported among 20% of the respondents, which is lower when compared to the results obtained in a previous study conducted among the physicians in Puerto Rico [31]. Nevertheless, the practice of prophylactic platelet transfusion is not recommended by the WHO guidelines [22]. In addition, recent studies revealed that prophylactic platelet transfusion does not improve platelet count. It might also lead to several adverse reactions [39] and an increased duration of hospital stay, which further leads to an increase in the total cost of treatment [40]. In the current study, most physicians failed to identify all the possible adverse effects of paracetamol. This could be because paracetamol is relatively safe when taken within the therapeutic dosage limits (<4 g per day in adults) and also because physicians tend to perceive paracetamol as less risky when compared to other analgesics or antipyretics [41].

In addition, it was observed that physician's knowledge on laboratory diagnosis of dengue fever was low. Only 21.52% of the respondents were able to identify all the diagnostic tests available for dengue fever. However, a study conducted among the physicians practicing in Puerto Rico [31] revealed that only 6% of them knew about the laboratory tests used to diagnose dengue fever. It is important to have a strong knowledge of the diagnostic parameters because early diagnosis of dengue fever decreases the morbidity and mortality rates associated with it [26][39][42]. Even though the WHO guidelines [22] do not recommend the use of corticosteroids, 13% of the respondents do not have the practice of advising patients to avoid steroids when diagnosed with dengue. It is important to instruct patients to avoid steroids because they are likely to increase the risk of upper gastrointestinal bleeding and stress ulceration [43]. In addition, a randomized controlled trial revealed that there is no sufficient evidence to justify the use of corticosteroids in the management of dengue shock syndrome [44].

3. Conclusions

Despite dengue fever being endemic in Bangladesh, India, and Malaysia, the clinical knowledge of physicians practicing in these countries is not optimal. This calls for a continued and sustained clinical training on dengue fever management.

Lower KAP scores among physicians in Turkey where the cases are limited. Future studies need to assess the impact of educational interventions on physician's knowledge and clinical management of dengue fever.

References

1. World Health Organization. Dengue and Severe Dengue. Available online: (accessed on 1 December 2020).
2. Bhatt, S.; Gething, P.W.; Brady, O.J.; Messina, J.P.; Farlow, A.W.; Moyes, C.L.; Drake, J.M.; Brownstein, J.S.; Hoen, A.G.; Sankoh, O.; et al. The global distribution and burden of dengue. Nature 2013, 496, 504–507.
3. Centers for Disease Control and Prevention. Dengue. Available online: (accessed on 1 December 2020).
4. Wong, L.P.; Alias, H.; Aghamohammadi, N.; Sam, I.C.; Abu Bakar, S. The Self-Regulation Model of Illness: Comparison between Zika and Dengue and Its Application to Predict Mosquito Prevention Behaviours in Malaysia, a Dengue-Endemic Country. Int. J. Environ. Res. Public Health 2016, 13, 1210.
5. Gubler, D.J. Dengue and dengue hemorrhagic fever. Clin. Microbiol. Rev. 1998, 11, 480–496.
6. Muller, D.A.; Depelsenaire, A.C.; Young, P.R. Clinical and Laboratory Diagnosis of Dengue Virus Infection. J. Infect. Dis. 2017, 215, S89–S95.
7. Ananth, S.; Shrestha, N.; Trevino, C.J.; Nguyen, U.S.; Haque, U.; Angulo-Molina, A.; Lopez-Lemus, U.A.; Lubinda, J.; Sharif, R.M.; Zaki, R.A.; et al. Clinical Symptoms of Arboviruses in Mexico. Pathogens 2020, 9, 964.
8. Pang, X.; Zhang, R.; Cheng, G. Progress towards understanding the pathogenesis of dengue hemorrhagic fever. Virol. Sin. 2017, 32, 16–22.
9. Ganeshkumar, P.; Murhekar, M.V.; Poornima, V.; Saravanakumar, V.; Sukumaran, K.; Anandaselvasankar, A.; John, D.; Mehendale, S.M. Dengue infection in India: A systematic review and meta-analysis. PLoS Negl. Trop. Dis. 2018, 12, e0006618.
10. Muraduzzaman, A.K.M.; Alam, A.N.; Sultana, S.; Siddiqua, M.; Khan, M.H.; Akram, A.; Haque, F.; Flora, M.S.; Shirin, T. Circulating dengue virus serotypes in Bangladesh from 2013 to 2016. Virusdisease 2018, 29, 303–307.
11. Pervin, M.; Tabassum, S.; Kumar Sil, B.; Islam, M.N. Isolation and Serotyping of Dengue Viruses by Mosquito Inoculation and Cell Culture Technique: An Experience in Bangladesh. 2003. Available online: (accessed on 3 March 2021).
12. Shekhar, K.C.; Huat, O.L. Epidemiology of dengue/dengue hemorrhagic fever in Malaysia—A retrospective epidemiological study. 1973–1987. Part II: Dengue fever (DF). Asia Pac. J. Public Health 1992, 6, 126–133.
13. Murphy, A.; Rajahram, G.S.; Jilip, J.; Maluda, M.; William, T.; Hu, W.; Reid, S.; Devine, G.J.; Frentiu, F.D. Incidence and epidemiological features of dengue in Sabah, Malaysia. PLoS Negl. Trop. Dis. 2020, 14, e0007504.
14. Schaffner, F.; Mathis, A. Dengue and dengue vectors in the WHO European region: Past, present, and scenarios for the future. Lancet Infect. Dis. 2014, 14, 1271–1280.
15. Oter, K.; Gunay, F.; Tuzer, E.; Linton, Y.M.; Bellini, R.; Alten, B. First record of Stegomyia albopicta in Turkey determined by active ovitrap surveillance and DNA barcoding. Vector Borne Zoonotic Dis. 2013, 13, 753–761.
16. Akiner, M.M.; Demirci, B.; Babuadze, G.; Robert, V.; Schaffner, F. Spread of the Invasive Mosquitoes Aedes aegypti and Aedes albopictus in the Black Sea Region Increases Risk of Chikungunya, Dengue, and Zika Outbreaks in Europe. PLoS Negl. Trop. Dis. 2016, 10, e0004664.
17. Gubler, D.J.; Reiter, P.; Ebi, K.L.; Yap, W.; Nasci, R.; Patz, J.A. Climate variability and change in the United States: Potential impacts on vector- and rodent-borne diseases. Environ. Health Perspect. 2001, 109 (Suppl. 2), 223–233.
18. Reiter, P. Climate change and mosquito-borne disease. Environ. Health Perspect. 2001, 109 (Suppl. 1), 141–161.
19. Teurlai, M.; Menkès, C.E.; Cavarero, V.; Degallier, N.; Descloux, E.; Grangeon, J.-P.; Guillaumot, L.; Libourel, T.; Lucio, P.S.; Mathieu-Daudé, F.; et al. Socio-economic and Climate Factors Associated with Dengue Fever Spatial Heterogeneity: A Worked Example in New Caledonia. PLoS Negl. Trop. Dis. 2015, 9, e0004211.
20. Gubler, D.J. Dengue, Urbanization and Globalization: The Unholy Trinity of the 21st Century. Trop. Med. Health 2011, 39, 3–11.
21. Ramos, M.M.; Mohammed, H.; Zielinski-Gutierrez, E.; Hayden, M.H.; Lopez, J.L.; Fournier, M.; Trujillo, A.R.; Burton, R.; Brunkard, J.M.; Anaya-Lopez, L.; et al. Epidemic dengue and dengue hemorrhagic fever at the Texas-Mexico border: Results of a household-based seroepidemiologic survey, December 2005. Am. J. Trop. Med. Hyg. 2008, 78, 364–369.

22. World Health Organization. Dengue, Guidelines for Diagnosis, Treatment, Prevention and Control. Available online: (accessed on 1 December 2020).

23. Senaratne, T.; Noordeen, F. Diagnosis of dengue in Sri Lanka: Improvements to the existing state of the art in the island. Trans. R. Soc. Trop. Med. Hyg. 2014, 108, 685–691.

24. Jasamai, M.; Yap, W.B.; Sakulpanich, A.; Jaleel, A. Current prevention and potential treatment options for dengue infection. J. Pharm. Pharm. Sci. 2019, 22, 440–456.

25. Lai, S.C.; Huang, Y.Y.; Shu, P.Y.; Chang, S.F.; Hsieh, P.S.; Wey, J.J.; Tsai, M.H.; Ben, R.J.; Hsu, Y.M.; Fang, Y.C.; et al. Development of an Enzyme-Linked Immunosorbent Assay for Rapid Detection of Dengue Virus (DENV) NS1 and Differentiation of DENV Serotypes during Early Infection. J. Clin. Microbiol. 2019, 57.

26. Doblecki-Lewis, S.; Chang, A.; Jiddou-Yaldoo, R.; Tomashek, K.M.; Stanek, D.; Anil, L.; Lichtenberger, P. Knowledge, attitudes, and practices of Florida physicians regarding dengue before and after an educational intervention. BMC Med. Educ. 2016, 16, 124.

27. Lee, L.K.; Thein, T.L.; Kurukularatne, C.; Gan, V.; Lye, D.C.; Leo, Y.S. Dengue knowledge, attitudes, and practices among primary care physicians in Singapore. Ann. Acad. Med. Singap. 2011, 40, 533–538.

28. Saringe, S.; Kajeguka, D.C.; Kagirwa, D.D.; Mgabo, M.R.; Emidi, B. Healthcare workers knowledge and diagnostic practices: A need for dengue and chikungunya training in Moshi Municipality, Kilimanjaro Tanzania. BMC Res. Notes 2019, 12, 43.

29. Mohammed Yusuf, A.; Abdurashid Ibrahim, N. Knowledge, attitude and practice towards dengue fever prevention and associated factors among public health sector health-care professionals: In Dire Dawa, eastern Ethiopia. Risk Manag. Healthc. Policy 2019, 12, 91–104.

30. Fahad Khan, S.K.; Tayyab, R.F.; Syeda, N.; Danish, K.; Mashmula, T.; Sanjay, K.; Afia, R.; Nadeem, C. Knowledge and management practices regarding dengue fever among doctors of tertiary care hospital. Int. J. Fam. Community Med. 2018, 2, 315–319.

31. Tomashek, K.M.; Biggerstaff, B.J.; Ramos, M.M.; Pérez-Guerra, C.L.; Garcia Rivera, E.J.; Sun, W. Physician Survey to Determine How Dengue Is Diagnosed, Treated and Reported in Puerto Rico. PLoS Negl. Trop. Dis. 2014, 8, e3192.

32. Ho, T.S.; Huang, M.C.; Wang, S.M.; Hsu, H.C.; Liu, C.C. Knowledge, attitude, and practice of dengue disease among healthcare professionals in southern Taiwan. J. Formos. Med. Assoc. 2013, 112, 18–23.

33. Brady, O.J.; Golding, N.; Pigott, D.M.; Kraemer, M.U.; Messina, J.P.; Reiner, R.C., Jr.; Scott, T.W.; Smith, D.L.; Gething, P.W.; Hay, S.I. Global temperature constraints on Aedes aegypti and Ae. albopictus persistence and competence for dengue virus transmission. Parasit Vectors 2014, 7, 338.

34. Johnson, T.L.; Haque, U.; Monaghan, A.J.; Eisen, L.; Hahn, M.B.; Hayden, M.H.; Savage, H.M.; McAllister, J.; Mutebi, J.-P.; Eisen, R.J. Modeling the Environmental Suitability for Aedes (Stegomyia) aegypti and Aedes (Stegomyia) albopictus (Diptera: Culicidae) in the Contiguous United States. J. Med. Entomol. 2017, 54, 1605–1614.

35. Kraemer, M.U.; Sinka, M.E.; Duda, K.A.; Mylne, A.Q.; Shearer, F.M.; Barker, C.M.; Moore, C.G.; Carvalho, R.G.; Coelho, G.E.; Van Bortel, W.; et al. The global distribution of the arbovirus vectors Aedes aegypti and Ae. albopictus. eLife 2015, 4, e08347.

36. Kraemer, M.U.G.; Sinka, M.E.; Duda, K.A.; Mylne, A.; Shearer, F.M.; Brady, O.J.; Messina, J.P.; Barker, C.M.; Moore, C.G.; Carvalho, R.G.; et al. The global compendium of Aedes aegypti and Ae. albopictus occurrence. Sci. Data 2015, 2, 150035.

37. Morales, I.; Salje, H.; Saha, S.; Gurley, E.S. Seasonal Distribution and Climatic Correlates of Dengue Disease in Dhaka, Bangladesh. Am. J. Trop. Med. Hyg. 2016, 94, 1359–1361.

38. Rao, P.N.; van Eijk, A.M.; Choubey, S.; Ali, S.Z.; Dash, A.; Barla, P.; Oraon, R.R.; Patel, G.; Nandini, P.; Acharya, S.; et al. Dengue, chikungunya, and scrub typhus are important etiologies of non-malarial febrile illness in Rourkela, Odisha, India. BMC Infect. Dis. 2019, 19, 572.

39. Lye, D.C.; Archuleta, S.; Syed-Omar, S.F.; Low, J.G.; Oh, H.M.; Wei, Y.; Fisher, D.; Ponnampalavanar, S.S.L.; Wijaya, L.; Lee, L.K.; et al. Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: A multicentre, open-label, randomised, superiority trial. Lancet 2017, 389, 1611–1618.

40. Sethi, S.M.; Khalil, A.; Naseem Khan, M.R.; Khatri, A.; Muhammad, A.J.; Murtaza, G. Clinical outcomes of prophylactic platelet transfusion in patients with dengue: A retrospective study of patients at a tertiary care hospital in Karachi. J. Pak. Med. Assoc. 2017, 67, 1374–1378.

41. Castillo-Guzman, S.; González-Santiago, O.; Delgado-Leal, I.A.; Lozano-Luévano, G.E.; Reyes-Rodríguez, M.J.; Elizondo-Solis, C.V.; Nava-Obregón, T.A.; Palacios-Ríos, D. Perception of the risk of adverse reactions to analgesics: Differences between medical students and residents. PeerJ 2016, 4, e2255.

42. Kalayanarooj, S. Clinical Manifestations and Management of Dengue/DHF/DSS. Trop. Med. Health 2011, 39, 83–87.
43. Rajapakse, S. Corticosteroids in the treatment of dengue illness. Trans. R. Soc. Trop. Med. Hyg. 2009, 103, 122–126.
44. Panpanich, R.; Sornchai, P.; Kanjanaratanakorn, K. Corticosteroids for treating dengue shock syndrome. Cochrane Database Syst. Rev. 2006, CD003488.