International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 7; Issue 7(D); July 2018; Page No. 14145-14149
DOI: http://dx.doi.org/10.24327/ijcar.2018.14149.2554

Research Article

CO-DISTRIBUTION AND CO-INFECTION OF DENGUE AND CHIKUNGUNYA VIRUSES- AN UNDERESTIMATED THREAT

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A R T I C L E I N F O

Article History:

Received 5th April, 2018
Received in revised form 24th May, 2018 Accepted 20th June, 2018
Published online 28th July, 2018

Key words:

Dengue, Chikungunya, Co-infection, Seroprevalence, Central India

A B S T R A C T

Introduction: Dengue and chikungunya are important mosquito-borne viral diseases of humans. In areas where both viruses co-circulate, they can be transmitted together.
Aim & Objectives: This study was conducted to know the prevalence of dengue and chikungunya and their co-infection as well to study clinical features.
Material and Methods: Blood samples were collected from clinically suspected cases of dengue and chikungunya infection and were tested for dengue IgM antibody, dengue NS1 antigen and chikungunya IgM antibodies by ELISA.
Results: Total 2153 samples for dengue, chikungunya and its co-infection were tested. 350 (16.26%) samples were found positive for dengue and 203 (09.43%) were found to be positive for chikungunya. Co-infection of dengue and chikungunya was found in 64 (02.97%) samples out of the 2153 samples. Adults in the age group of 21 years to 30 years were affected higher than any other age group in dengue, chikungunya and their co - infection. Males were affected more than females in dengue infection while in chikungunya; Rash, haemorrhagic manifestations and thrombocytopenia were more common in dengue fever and chikungunya infection was commonly presented with arthralgia and leucocytosis. Severe VAS score was seen in mono chikungunya and co-infection.
Conclusion: Dengue and chikungunya viruses can cause dual infections in humans, resulting in illness with overlapping signs and symptoms, making diagnosis and treatment difficult. Hence, clinically suspected cases should be tested for both the pathogens in the endemic areas.

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INTRODUCTION

Viruses are dynamic players in the ecology of the planet as they cause sufferings, diseases and deaths among human population. With wide distribution in tropical and subtropical areas throughout the world, chikungunya virus (CHIKV) and dengue virus (DENV) cause acute febrile illnesses characterized by arthralgia. [1] CHIKV has recently caused large epidemics and DENV is a global plague, with tens of millions of cases each year. [1,2]

DENV and CHIKV are positive-sense, single-stranded RNA viruses. DENV belongs to the family Flaviviridae and genus *Flavivirus* with 5 known serotypes (DENV1–5). CHIKV belongs to the family Togaviridae and genus *Alphavirus* with 3 known strains (Asian-West African; East-Central; South African).[3] The genome of each virus is approximately 11 kb in length. [3, 4] The DENV genome encodes three structural (C, prM, and E) and seven nonstructural (NS1, NS2B, NS3, NS4A, NS4B, and NS5) proteins. [5]

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The CHIKV genome encodes three structural (C, E1, and E2) and four nonstructural (nsP1–4) proteins. [3]

Both DENV and CHIKV viruses are arthropod-borne viruses (arboviruses) with a common vector: mosquitos of the *Aedes* genus, specifically *A. aegypti* and *A. albopictus.* [6] The most commonly affected people of DENV and CHIKV infections are those residing in endemic areas, which include most of the tropical and subtropical regions worldwide. Many of these are popular tourist destinations and consequently, dengue-related infections have recently surpassed malaria and gastrointestinal infections as the most common cause of febrile illness among travelers. [7] The major endemic regions include Southeast Asia, the Western Pacific, the Eastern Mediterranean, Africa, and the Americas. [8] In India, dengue and chikungunya are endemic in most major states like Goa, Gujarat, Karnataka, Kerala, Haryana, Madhya Pradesh, Punjab, Maharashtra, Rajasthan, Tamil Nadu, Uttar Pradesh, West Bengal, Chandigarh, Delhi and Puducherry. [9]

DENV and CHIKV are transmitted by the same *Aedes* spp. mosquitoes, so it is a reasonable expectation that the epidemiology of both infections is temporally and spatially related. Moreover, because symptoms presented by infected

patients are similar and with symptomatological diagnosis, there is an inevitably ambiguity in disease recognition and so in areas where DENV circulates, CHIKV remains undiagnosed. While they present similarly, they have vastly different management strategies and outcomes. [10] This mandates laboratory tests to distinguish between these two diseases.

Over the past few years, although chikungunya is being reported as a co-infection with dengue in several parts of India, very few studies are available. Therefore, the present study was conducted to 1. know the seroprevalence of dengue and chikungunya co-infection and 2. study the clinical features of dengue and chikungunya co-infection and to compare it with chikungunya and dengue mono-infection.

MATERIAL AND METHODS

The present observational cross-sectional study was carried out in department of Microbiology at a tertiary care hospital, in central India which is a sentinel surveillance site under National Vector Borne Disease Control Programme (NVBDCP) from January 2016 to December 2017. Approval was obtained from the intuitional ethical committee. Study group consisted of 2153 clinically suspected cases of dengue and chikungunya infection of both the sex and all age group, admitted in the hospital as well as those who attended outpatient department. Detailed history was obtained from each patient.

Blood was collected for complete blood counts, erythrocyte sedimentation rate, peripheral smear for malarial parasites, rapid malarial antigen test, leptospira rapid test, dengue and chikungunya enzyme-linked immune sorbent assay (ELIZA). The number of tender and swollen joints was recorded in the first visit. The Visual Analogue Scale (VAS) for joint pain was measured from 0 – 10 (0 indicating no pain in joints, 10 indicating maximum pain) on day 0 and day 15 (in all patients) and then every monthly in patients who had persistent joint pains.

Serum was separated from the blood as per the standard guidelines. [11,12] Specimens were stored at 2-8°C till processing. Repeated freezing and thawing was avoided.

The serum samples were subjected to following tests for the diagnosis of dengue and chikungunya infection –

1. Dengue NS1 antigen detection with ELISA
2. Dengue IgM antibody detection with ELISA
3. Chikungunya IgM antibody detection with ELISA

Dengue NS1 antigen MICROLISA kit was provided by J. Mitra and Co. Pvt. Ltd. India. NIV DEN IgM Capture ELISA (MAC ELISA) kit and NIV CHIK IgM Capture ELISA kit were provided by NIV, Pune , India. Tests were performed as per manufacturer's instructions only.

Patients with fever duration < 5 days were tested for dengue NS1 antigen by ELISA and those with fever duration ≥ 5 days were tested for dengue IgM antibody by ELISA. Chikungunya IgM antibody detection by chikungunya ELISA was performed on all samples.

RESULTS

In present study, we tested total 2153 samples for dengue, chikungunya and its co-infection. A total of 350 (16.26%) samples were found positive for dengue. Out of 350 samples positive for dengue, 69 were positive by NS1 antigen detection test, 275 were positive by IgM antibody detection test and 06 were positive for both dengue IgM antibody and NS1 antigen (Figure 1). Out of the 2153 samples, 203 were found to be positive for chikungunya IgM antibody. Co-infection of dengue and chikungunya was found in 64 (02.97%) samples out of the 2153 samples tested. (Table 1) Adults in the age group of 21-30 years were affected higher than any other age group in dengue, chikungunya and their co-infection. Age wise distribution is shown in table-2. Males were affected more than females in dengue infection while in chikungunya, females were more affected more than males. Gender distribution is shown in table-3. The charcteristic clinical features of acute mono dengue and chikungunya infection and dengue with chikungunya co-infection are compared in table 4.

Among the mono and dual infections, all 139 (100%) mono CHIKV and 54 (84.38%) of dual infections showed severe VAS score of 6-10, while in case of mono DENV, only 89 (31.12%) of patients showed severe VAS scores as seen in Figure 2.

DISCUSSION

Until now, the number of laboratory confirmed cases of DENV-CHIKV co-infections is surprisingly small and available information is often inadequate, further making it difficult to establish baseline epidemiological trends. However, it is noteworthy that the number of reported cases has increased considerably during the past 10 years indicating that the phenomenon is becoming a concern among the scientific community because of its potential impact on human health and economy.[13]

Indeed, although the first cases of dengue-chikungunya co-infection were reported in Thailand by Nimmannitya *et al* (1969) [14] and in 1964, co-infection cases were also reported in Vellore, south India [15, 16] during a spate of chikungunya epidemics spanning 1963–1973 [17] it was not until 2006 that the diagnosis of concomitant infections experienced a real interest, possibly due to the burden of cases of chikungunya infection in the Indian Ocean's island and Southeast Asia where DENV is endemic.

In the present study, co-infection of dengue and chikungunya was found in 64 (02.97%) out of the 2153 samples. This is in accordance with other studies. Dengue and chikungunya co-infection prevalence among the various studies carried out are shown in table-5.

The vectors for transmission of dengue and chikungunya are *A. aegypti* and *A. albopictus* mosquitoes. Since both dengue and chikungunya viruses are transmitted through a common vector, they often co-circulate in the mosquito. [6,22] A study conducted by Potiwat *et al* (2011) [23] supports two modes of mosquito co-infection that have been suggested to occur in natural conditions: a mosquito could get co-infected by ingesting its blood meal from a viremic individual carrying both viruses or sequentially by ingesting the blood from two different individuals each infected by a single virus with the quantity of one of the viral species not overwhelmingly exceeding the other one to avoid any competitive suppression. [23]

The mode by which these viruses can be transmitted to humans is another important topic related to CHIKV/DENV co-

infections, is. Two main possibilities could be envisaged for transmission of these viruses to humans either through an individual transmission of each virus by different mono-infected mosquitoes or with concomitant transmission by a co-infected vector. [13] The viral RNA of both viruses can be detected in the blood of co-infected humans, suggesting that they are both able to concomitantly invade, replicate and spread in different organs to establish a systemic infection resulting in viremia. Thus, these viruses seem to have adopted different replicative strategies to overcome the potential competition for cellular resources when they infect the same mammalian cells, and/or have established cooperative interactions to guarantee their survival and propagation in human hosts. [13]

In our study, highest positivity of dengue is seen in adult age group of 21-30 years (49.65%), followed by 11-20 years (22.38%). For chikungunya also, positivity rate is higher in 21-30 (34.53%) years of age group. Our findings are in accordance with Kumar A *et al* (2010), Ukey PM *et al* (2010) and Tomar A *et al* (2017). [24-26]

In the present study, males were affected more than females in dengue infection, which is reverse in case of chikungunya and dengue chikungunya co-infection as shown in table 3. Sex ratios of cases suffering from dengue, chikungunya and co-infection were observed as 1.23:1, 0.86:1 and 0.73:1 respectively. Similar findings have been reported by Modi KP *et al* (2017) [10] and Burve S *et al* (2013). [27] Women have been notably more affected than men, which may be explained with the cultural custom of women to work at home, where the main vector (*A. aegypti*) of chikungunya (CHIKV) sets, usually associated with deposits of water which have day biting habit. [27,28]

As seen in table 4, patients of dengue mono infection had significant difference in myalgia, rash, hemorrhagic manifestations and thrombocytopenia as compared to DENV and CHIKV co-infected patients; whereas arthritis-like illness was more common in DENV and CHIKV co-infection and mono CHIK infection. We can therefore say that the presence of rash and hemorrhagic manifestations can be used clinically to differentiate the diagnosis of DENV mono-infection from DENV and CHIKV co -infection.

In the present study, leucopenia was more commonly observed in patients with DENV infection as compared with CHIKV infection. In contrast patients infected with CHIKV mono -infection had a normal or elevated WBC count. This can be used as a one of the laboratory parameters to differentiate DENV infection from CHIKV infection. Presence of thrombocytopenia was more in patients of dengue as compared with mono or dual infections with CHIKV or CHIKV+ DENV. These results are similar to those reported by Vernon Lee *et al* (2012). [29]

VAS is a uni-dimensional measure of pain intensity. The pain VAS is self completed by the respondent. Using a ruler, the score is determined and higher score indicates greater pain intensity. In the present study, among the mono and dual infections, all 139 (100%) mono CHIKV and 54 (84.38%) of dual infections showed severe VAS score of 6-10, while in case of mono DENV, only 89 (31.12 %) of patients showed severe VAS scores as seen in figure 2. Similar findings have been reported in other studies. In Londhey V *et al* (2016) [22], among the mono and dual infections, all mono CHIKV and 90% dual infections showed severe VAS score of 6-10, however in mono DENV, only 55% of patients showed severe VAS score. Some part of this finding was reproduced in Galate *et al* (2016) where all CHIKV infected patients had VAS score between 6-10 and only 15.78% of dual infected patients had VAS score less than 6.[30] This particular finding can be used to differentiate dengue mono infection from dual infection and chikungunya mono infection.

From a public health perspective, the concern about co-infections is their possible impact on the pathogenesis and the outcome of dengue and chikungunya diseases. Is there a correlation between the cases of co-infection and the severity of symptoms? Because, as it is known in terms of morbidity, severity and mortality DENV has a significant impact on human health in comparison to CHIKV, the concerning issue is that CHIKV/DENV co-infection could increase the incidence of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[13] Several studies have been done to describe the severity of dengue-chikungunya co-infection. Two studies, Chahar *et al* (2009) [31] and Gandhi *et al* (2015) [32] have described increased severity with co-infection. The mortality rate in Gandhi *et al* was 12% in co-infected patients as compared to 2% in mono-infected patients [32]. In the present study, mortality rate in co-infected patients was 10.94% as compared to 1.39% in mono-infection. However, various other studies did not report any increase in mortality with co-infection [21,33] making the situation unclear. Indeed, the available data is not enough to conclude if the concomitant infection by both viruses is able to aggravate the clinical symptoms caused by DENV and CHIKV mono infections. A systematic and larger clinical survey should be done to assess if co-infections are associated to severe forms of dengue and chikungunya diseases as clinical studies may justify further research on the pathogenesis of CHIKV/DENV co-infections to understand the immunological events that are triggered.

The need to differentiate between two infections is also very important because of minute differences in treatment and misdiagnosis can hamper epidemiological understanding of both diseases. With the misdiagnosis of dengue fever as chikungunya (or missing a dengue infection when co-inciding with chikungunya) there is always a risk of delay or disruption in dengue-specific intensive supportive treatment which can have a ten-fold impact on likelihood of progression from dengue fever to severe disease. It also risks inappropriate prescription of arthralgia-alleviating non-steroidal anti-inflammatory drugs (often employed in treating chikungunya patients) which could lead to severe bleeding in patients with thrombocytopenia or DHF. However, chikungunya infection being misdiagnosed as dengue (or missed in a co-infected individual) is most likely, which masks the true geographical extent of CHIKV and population at risk of infection. [34,35]

CONCLUSION

Findings in current study clearly show that CHIKV co-circulates with DENV and causes many intersecting symptoms with very few unequalled symptoms which can help to certain the diagnosis. Hence, understanding those subtle clinical manifestations would enable in better patient management. It is also equally important to test clinically suspected cases for both the viruses in the endemic areas. Formation of protocols using clinical and laboratory measures to correctly diagnose the illness would be helpful so that proper laboratory and

molecular diagnostic measures can be used in each patient in a cost effective manner. For identification and characterization of these viral pathogens enhanced and continuous surveillance for both dengue and chikungunya viruses is equally essential in the endemic areas. This information will also help in the execution of proper measures to control the outbreaks caused by these emerging viral pathogens.

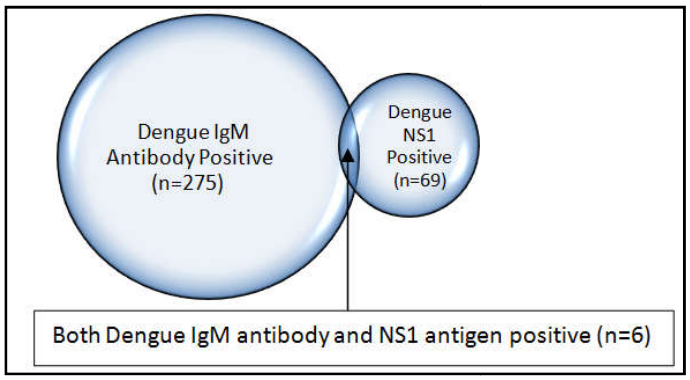

Figure 1 Distribution of IgM antibody and NS1antigen positive cases by ELISA

Table 1 Positivity of dengue, chikungunya and co-infection

	Dengue	Chikungunya	Co-infection
Dengue NS1 Antigen Positive	63	-	06
Dengue IgM Antibody Positive	223	-	58
Chikungunya IgM Antibody Positive	-	139	64
Total	286	139	-

Table 2 Age wise distribution of dengue, chikungunya and co-infection in positive cases

Age (Yrs)	Number Of Samples	Dengue (%)	Chikungunya (%)	Co-Iinfection (%)
0-10	456	52 (18.19)	19 (13.67)	04 (06.25)
11-20	611	64 (22.38)	21 (15.11)	12 (18.75)
21-30	646	142 (49.65)	48 (34.53)	29 (45.31)
31-40	241	17 (05.94)	31 (22.30)	11 (17.18)
41-50	109	09 (03.15)	11 (07.91)	06 (09.38)
51-60	54	00	04 (02.88)	00
>60	39	02 (00.69)	05 (03.60)	02 (03.13)
Total	2156	286	139	64

Table 3 Gender wise distribution of dengue, chikungunya and co-infection in positive cases

	Dengue (%)	Chikungunya (%)	Co-infection (%)
Male	158 (55.24)	63 (45.32)	27 (42.19)
Female	128 (44.76)	76 (54.68)	37 (57.81)
Total	286	139	64

Table 4 Comparison between clinical features of dengue, chikungunya and co-infection in positive cases

Clinical Features	Dengue (%)	Chikungunya (%)	Co-infection (%)
Fever	286 (100)	139 (100)	64 (100)
Myalgia	231 (80.77)	97 (69.78)	34 (53.12)
Headache	159 (55.59)	88 (63.31)	48 (75.00)
Joint Pain	163 (56.99)	139 (100)	64 (100)
Rash	47 (16.43)	03 (02.16)	03 (04.69)
Vomitting	19 (06.64)	02 (01.44)	01 (01.56)
Diarrhoea	07 (02.45)	02 (01.44)	01 (01.56)
Hepatomegaly	21 (07.34)	01 (00.72)	02 (03.13)
Lymphadenopathy	14 (04.89)	01 (00.72)	02 (03.13)
Haemorrhagic Manifestation	31 (10.84)	01 (00.72)	02 (03.13)
Dysponea	23 (08.04)	03 (02.16)	08 (12.50)
Circulatory failure	15 (05.24)	01 (00.72)	02 (03.13)
Death	04 (01.39)	00	07 (10.94)
Laboratory Findings			
Anaemia	143 (50.00)	48 (34.53)	23 (35.94)
Leukopenia	157 (54.89)	00	02 (03.13)
Thrombocytopenia	178 (62.24)	56 (40.29)	33 (51.56)
Elevated Liver Enzymes	89 (31.12)	09 (06.47)	14 (21.88)

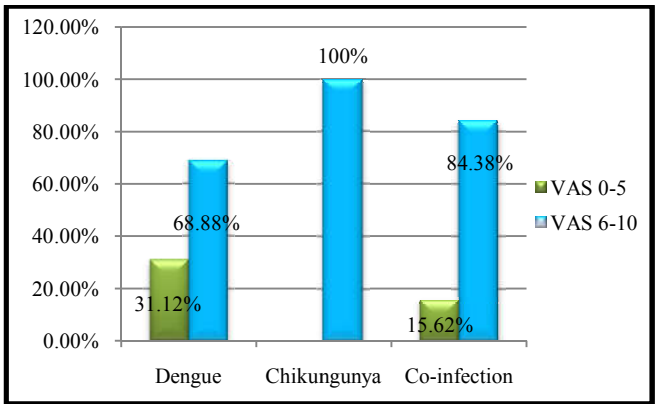

Figure 2 VAS in patients with joint pain

Table 5 Prevalence of dengue and chikungunya co-infection among the various studies conducted in India

References	Year	Location	Prevalence of Co- Infection (%)
Gunasekaran P *et al* [18]	2010	Tamil Nadu	5.5
Kalawat U *et al* [19]	2011	South India	2.7
Mohanty I *et al* [20]	2011-12	Southern Odisha	1.2
Taraphdar D *et al* [21]	2012	West Bengal	12.4
Modi KP *et al* [10]	2013	Gujarat	3.9
Londhey V *et al* [22]	2010-15	Mumbai	6.7
Present study	2016-2017	Central India-Maharashtra	2.97

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How to cite this article:

Smita Deshkar, Rajani Tore and Sharmila Raut (2018) 'Co-Distribution and Co-Infection of Dengue and Chikungunya Viruses- An Underestimated Threat', *International Journal of Current Advanced Research,* 07(7), pp. 14145-14149.
DOI: http://dx.doi.org/10.24327/ijcar.2018.14149.2554

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