MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-3238) Vol. 3(2) pp. xxx-xxx, February, 2015
Available online http://www.meritresearchjournals.org/mms/index.htm
Copyright © 2015 Merit Research Journals

Original Research Article

Chikungunya fever among children presenting with nonspecific febrile illness during an epidemic of dengue fever in Lahore, Pakistan

Muhammad Faheem Afzal[1*], Syed Qasim Naqvi[2], Muhammad Ashraf Sultan[3] and Asif Hanif[4]

[1]Assistant Professor, Department of Paediatrics, King Edward Medical University/ Mayo Hospital, Lahore, Pakistan

[2]Post Graduate Resident, Department of Paediatrics, King Edward Medical University/ Mayo Hospital, Lahore, Pakistan

[3]Chairman and Professor Paediatrics, Department of Paediatrics, King Edward Medical University/ Mayo Hospital, Lahore, Pakistan)

[4]Assistant Professor and Head of Department of Biostatistics, PGMI Gulab Devi Hospital, Lahore, Pakistan)

***Corresponding Author's Email:** mfaheem169@yahoo.com

Abstract

Dengue fever and Chikungunya fever are caused by arbovirus. Human infection with either virus is associated with fever, arthralgia, malaise, headache, and rash. This study was conducted to determine the frequency of chikungunya fever among children presenting with non-specific febrile illness during an epidemic of dengue in Lahore, Pakistan. This cross sectional study was conducted in the Department of Paediatrics, King Edward Medical University/ Mayo Hospital, Lahore, Pakistan. A total of 75 children of age <12 years with nonspecific febrile illness, consistent with clinical case definition of dengue fever and chikungunya fever, were enrolled via consecutive sampling from May to October, 2011. All cases were subjected to serum samples for dengue and Chikungunya IgM and IgG (ELIZA) both in acute & convalescent phase. Among 75 children presenting with nonspecific febrile illness fulfilling clinical case definitions of dengue and chikungunya fever, 36 patients were confirmed; 3 cases of chikungunya fever and 33 cases of dengue fever. Rash remained the most common feature in children with both dengue and chikungunya fever, and was evident in 52% and 66% of patients respectively. Arthralgia and myalgia were more common in children with chikungunya fever. Leucopenia and thrombocytopenia were found in 34% and 75% cases of dengue fever, and in 66% and 100% cases with Chikungunya fever respectively. A 4% of cases had chikungunya fever during an epidemic of dengue fever in Lahore, Pakistan. Arthralgia and myalgia were more common in children with chikungunya fever. The presence of cases warrants that a high index of suspicion for chikungunya fever is kept during the epidemic of dengue in our region.

Key words: Children, Chikungunya fever, Dengue fever, Epidemic, Fever, Non-specific febrile illness

Abbreviations: CHIKV: Chikungunya virus; **CHIKF:** Chikungunya fever; **DENV:** Dengue virus; **DF:** Dengue fever; **DHF:** Dengue Haemorrhagic Fever; **ELIZA:** Enzyme-Linked Immunosorbent Assay; **SPSS:** Statistical Package for Social Sciences; **WHO:** World Health Organization

INTRODUCTION

Chikungunya fever (CHIKF) is a viral illness caused by chikungunya virus (CHIKV) of the genus alphavirus of the family togaviridae. The disease is characterized by fever and severe joint pain (WHO, 2012). Other symptoms include muscle pain, headache, nausea, fatigue and rash. CHIKF is not a life threatening infection and never runs into a stage of shock. Symptomatic treatment for mitigating pain and fever using anti-inflammatory drugs

along with rest and reassurance usually suffices (Staples et al., 2009). Both dengue and CHIKV spread through the bite of infected *Aedes* mosquitoes. The disease resembles dengue fever (DF). Nimmannitya et al. (Nimmannitya et al., 1969) and Simon et al (Simon et al 2011) have compared the clinical and laboratory features in patients with CHIKF and DF.

CHIKV was first isolated between 1952-53 in Tanzania from both man and mosquito during an epidemic of fever that was considered clinically indistinguishable from dengue(hertz et al,2012). CHIKF displays interesting epidemiological profiles. Major epidemics appear cyclically, usually with an inter-epidemic period of 7-8 years and sometimes as long as 20 years. Between 1960 and 1982, outbreaks of CHIKF were reported from Bangkok (1960), India (1964), Sri Lanka (1969), Vietnam (1975), Myanmar (1975) and Indonesia (1982) (WHO, 2006). Risk of spread of dengue virus (DENV) and CHIKV has shown an increase in recent years due to various factors in urban, peri-urban and rural areas, leading to constant exchange of viruses which results in concurrent episodes of DF and CHIKF(Directorate,2012). The explosive epidemics of CHIKF in Indian Ocean islands and India since 2004 and the worldwide increase in travel have facilitated the spread of CHIKV in areas where DENV is endemic. As a result, co-circulation of CHIKV and DENV has been reported in various geographic areas, including India, Sri Lanka, Gabon, Cameroon, Madagascar, Malaysia, Indonesia, Singapore, and Thailand(Chang et al,2010).

Dengue virus has been active in Asian region since long · Pakistan first reported an epidemic of DF in 1994(Akram wt al,2005). Subsequent episodes occurred in 2005-6 (Pasha et al,2005) in Karachi and 2008 in Punjab(Javed et al,2009). In 2011, Pakistan experienced the world's largest reported epidemic of DF in Lahore. This epidemic largely involved the adult population. Thrombocytopenia was an unusually common finding during the epidemic(Hayat et al,2011). Co-occurrence of DF and CHIKF had formerly been observed in Maharashtra state of India, highlighting the importance of strong clinical suspicion and efficient laboratory support. Both DENV and CHIKF virus share common vector, geographical distribution, seasonal trend and clinical features, therefore rendering laboratory diagnosis critical in order to establish the cause of fever and initiate specific public health response.

Little work has been done to characterize the role of CHIKV as a cause of non-specific febrile illnesses during epidemic of DF in Pakistan. Given further that CHIKV is active in a neighboring country and that there are reports of co-occurrence of both the viruses in endemic regions, this study was conducted to determine the frequency of chikungunya fever among children presenting with non-specific febrile illness during an epidemic of dengue fever in Lahore, Pakistan.

MATERIAL AND METHODS

Study setting, participants and procedure

The cross sectional study was conducted from May to October 2011 during DF epidemic in the department of Pediatrics at Mayo Hospital/King Edward Medical University, Lahore, Pakistan. Informed consent was obtained from the parents of the children.

A consecutive sampling technique was used to enroll a total of 75 children <12 years of age with nonspecific febrile illness consistent with clinical case definitions of DF and CHIKF. Demography and clinical features were recorded on pretested proforma. A 2ml non-heparinized venous blood sample was taken both in acute & convalescent phase and serum was centrifuged. Serum was stored at -80°C and was transported on dry ice to the reference immunology laboratory. Serum samples were tested for anti-dengue and anti-chikungunya immunoglobulin M (IgM) and IgG antibodies using an enzyme-linked immunosorbent assay (ELISA). The Human ELISA kit was used and serology was determined by calorimetric detection method

Study definitions

"Dengue Fever (WHO, 2011)

Probable diagnosis

Acute febrile illness with two or more of the following: headache, retro-orbital pain, myalgia, arthralgia/bone pain, rash, haemorrhagic manifestations, leucopenia (WBC ≤5000 cells/mm3), thrombocytopenia (platelet count <150 000 cells/mm3), rising haematocrit (5 – 10%); and at least one of following: supportive serology on single serum sample: titre ≥1280 with haemagglutination inhibition test, comparable IgG titre with enzyme-linked immunosorbent assay, or testing positive in IgM antibody test, and occurrence at the same location and time as confirmed cases of dengue fever.

Confirmed diagnosis

Probable case with at least one of the following: isolation of dengue virus from serum, CSF or autopsy samples., fourfold or greater increase in serum IgG (by haemagglutination inhibition test) or increase in IgM antibody specific to dengue virus., detection of dengue virus or antigen in tissue, serum or cerebrospinal fluid by immunohistochemistry, immunofluorescence or enzyme-linked immunosorbent assay., detection of dengue virus genomic sequences by reverse transcription-polymerase chain reaction."

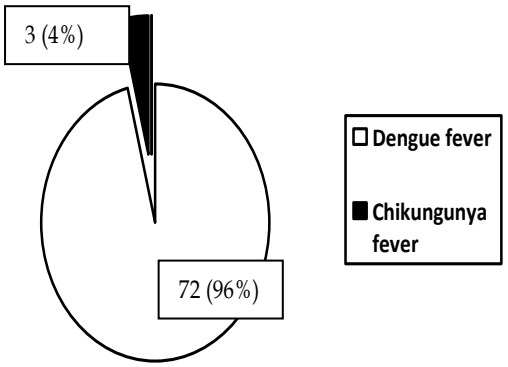

Figure Ia: Frequency of chikungunya cases among non-specific febrile children (n=75)

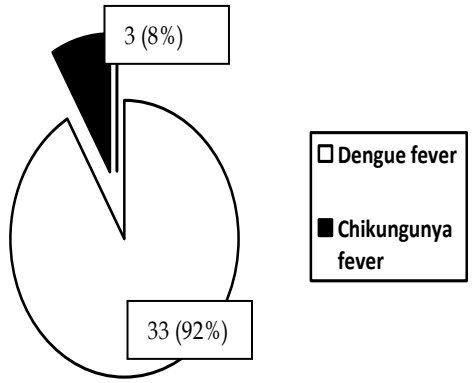

Figure Ib: Frequency of chikungunya cases among confirmed cases (n=36)

Table 1. Demographic variables (n=36) (Dengue n=33, Chikungunya n=03)

Variable	Dengue(%)	Chikungunya (%)	Total (%)	p value
Age (in Years)				
< 2 year	02(05)	00(00)	02(06)	0.977
2-5 years	12(37)	01(33)	13(36)	
>5-12 years	19(58)	02(66)	21(58)	
Sex				
Male	19(58)	03(100)	22(61)	0.183
Female	14(42)	00(00)	14(39)	
Total	33(100)	03(100)	36(100)	

"Chikungunya fever (Akram et al., 2005)

Probable case

Acute onset of fever >38.5°C and severe arthralgia/arthritis not explained by other medical condition

Confirmed Case

At least **one** of the following tests in the acute phase: virus isolation., presence of viral RNA by RT-PCR., presence of virus specific IgM antibodies in single serum sample collected in acute or convalescent stage., four-fold rising of IgG titers in samples collected at least three weeks apart."

Statistical analysis

Data was entered using statistical package for social sciences (SPSS) and subsequently analyzed. Descriptive statistics were presented as frequency tables. Chi square test was applied to compare differences.

RESULTS

Among 75 children presenting with nonspecific febrile illness fulfilling clinical case definition of both DF and CHIKF, 36 patients were confirmed; 3 cases of CHIKF and 33 cases of DF (Figure 1a and 1b)

Majority (58%) were 5-12 years of age. The mean age was 6±2 years. Males were predominant (61%). (Table 1). Rash remained the most common feature in children with both DF and CHIKF, and was evident in 52% and 66% of patients respectively. Arthralgia and myalgia were more common in children with CHIKF. Leucopenia and thrombocytopenia were found in 34% and 75% cases of DF, and in 66% and 100% cases with CHIKF respectively. (Table 2 and 3)

DISCUSSION

To our knowledge, this study is the first to prospectively investigate the role of CHIKV during epidemic of DF in

Table 2. Clinical variables (n=36) (Dengue n=33, Chikungunya n=03)

Clinical Features	Dengue (%)	Chikungunya (%)	Total (%)	p value
Rash	17(52)	02(66)	19(53)	0.39
Abdominal pain	11(34)	02(66)	13(36)	0.449
Arthralgia	15(46)	03(100)	18(50)	0.002
Myalgia	08(25)	03(100)	11(31)	0.02
Coryza	02(06)	01(33)	03(08)	0.16
Nausea/Vomiting	14(43)	02(66)	16(44)	0.66
Fatigue	12(37)	02(66)	14(38)	0.316
Retro orbital pain	07(22)	00(00)	07(19)	0.533
Headache	13(40)	02(66)	15(42)	0.35
Flushing	01(03)	00(00)	01(02)	0.96
Jaundice	00(00)	00(00)	00(00)	-
Hepatomegaly	13(40)	01(33)	14(38)	0.669
Positive Tourniquet Test	04(13)	01(33)	05(14)	0.06
Petechae	03(09)	01(33)	04(11)	0.14

Table 3. Laboratory variables (n=36) (Dengue n=33, Chikungunya n=03)

Variable	Dengue (%)	Chikungunya (%)	Total (%)	p value
Hematocrit				
<35	27(82)	02(66)	29(81)	0.791
35-45	06(18)	01(33)	07(19)	
WBC count				
<5000	11(34)	02(66)	13(36)	0.339
5000-11000	22(67)	01(33)	23(64)	
>11000	03(09)	00(00)	03(08)	
Platelets count				
<50,000	05(16)	01(33)	06(16)	0.121
50000-100000	06(19)	02(66)	08(22)	
100000-150000	13(40)	00(00)	13(36)	
>150000	12(36)	00(00)	12(33)	

Lahore, Pakistan. Our study shows that the 3 (4%) cases of CHIKF explained previously unrecognized causes of fever during the epidemic of DF. This is in contrast to global and regional data. Thiberville et al (Thiberville et al., 2013) reported 12% chikungunya fever from south west Indian ocean while Tanzania (Hertz et al., 2012) had 8% Chikungunya cases. India reported up to 45% attack rates from chikungunya virus in the affected states (Andhra Pradesh, Andaman & Nicobar Islands, Tamil Nadu, Karnataka, Maharashtra, Gujarat, Madhya Pradesh, Kerala and Delhi) (WHO,2006). The difference might be due to smaller sample size in our study. In this study, the majority belonged to the 5-12 years age group, with mean age 6.5±2 years. This is comparable to Hertz et al(Hertz et al, 2012) during recent outbreaks in Tanzania.

In our study, the most common feature in children with both DF and CHIKF was rash. Arthralgia and myalgia were more common in children with CHIKF, which is comparable with the results from Nimmannitya et al (Nimmannitya et al.,1969), Hertz et al (Hertz et a.l, 2012), Thiberville et al (Thiberville et al., 2013) and Kularatni et al (Kularatni et al., 2009) who reported similar results in outbreak setting. In present study, leucopenia was found comparably in both DF and CHIKF while thrombocytopenia was more common in CHIKF as 36% of DF patients had normal platelet counts. However, Kularatni et al (Kularatni et al., 2009) and Halstead et al(Halstead et al., 1969) reported less frequent thrombocytopenia in patients with CHIKF.

In our study, clinical signs and symptoms were largely unhelpful in distinguishing patients with CHIKV infection from dengue patients. This finding was consistent with a study conducted during a CHIKF outbreak in Reunion Island, underscoring the challenges of diagnosing CHIKV infection in the absence of laboratory diagnostic capacity. (Staikowsky, 2009)

Strengths and limitations

We believe that this is the first report of CHIKF from Pakistan during the epidemic of DF. Small number of patients with CHIKF is the major limitation of the study, due to which we are unable to compare and generalize the results.

CONCLUSION

Cases of chikungunya fever during an epidemic of dengue fever in Lahore, Pakistan, amounted to 4% of total cases. Arthralgia and myalgia were significant features in children with chikungunya fever. Though not many cases of CHIKF were found during the epidemic, those found warn us to keep a high index of suspicion for chikungunya.

RECOMMENDATIONS

Since CHIKV and DENV share the same vector, a high index of suspicion for CHIKF should be maintained during DF epidemics. Greater awareness of the prevalence of arboviral infections among clinicians and the availability of a reliable and affordable diagnostic test would improve patient management and contribute towards more accurate assessment of disease burden in Pakistan.

ACKNOWLEDGEMENT

The authors acknowledge the contribution of patients who volunteered themselves for the study.

Ethical approval and Funding

This study was approved by Ethical Review Board and was funded by King Edward Medical University, Lahore, Pakistan.

Conflict of interest

There was no conflict of interest between authors.

REFERENCES

Akram DS, Ahmad S. Dengue F (2005). Infect Dis J;14(4):124-5.

Chang SF, Su CL, Shu PY, Yang CF, Liao TL, Cheng CH et al., (Provide names of other authors) (2010). Concurrent isolation of chikungunya virus and dengue virus from a patient with coinfection resulting from a trip to Singapore. J Clin Microbiol;48:4586-9.

Directorate of National vector-borne disease control programme (2012). Mid term plan for prevention and control of dengue and chikungunya. http://www.nvbdcp.gov.in/Doc/Mid-Term-Plan-Dengue-Chikungunya-%202011-13.pdf

Halstead SB, Udomsakdi S, Singharaj P, Nisalak A (1969). Dengue and chikungunya virus Infection in man in Thailand, 1962–1964: III. Clinical, epidemiologic, and virologic observations on disease in non-indigenous white persons. Am J Trop Med Hyg;18:984-96.

Hayat AS, Baloch GH, Shaikh N (2011). Dengue infection: study for evaluation of enzyme immunoassay (EIA) test for rapid diagnosis. Professional Med J; 18:687-92.

Hertz JT, Munishi OM, Ooi EE, Howe S, Lim WY, Chow A, et al., (Provide names of other authors) (2012). Chikungunya and dengue fever among hospitalized febrile patients in Northern Tanzania. Am J Trop Med Hyg; 86:171-77.

Javed FT, Javed TA, Yusuf NW, Mannan A, Akram J, Sheikh UN et al., (Provide names of other authors) (2009). Prevalence of all four dengue virus serotypes confirmed by using real time RT-PCR among population of Lahore Pakistan. IJAVAMS;3:1-3.

Kularatne SA, Gihan MC, Weerasinghe SC, Gunasena S (2009). Concurrent outbreaks of chikungunya and dengue fever in Kandy, Sri Lanka, 2006-07: a comparative analysis of clinical and laboratory features. Postgrad Med J;85(1005):342-6.

Nimmannitya S, Halstead SB, Gohen SN, Margotta MR (1969). Dengue and chikungunya virus infection in Thailand 1962–64: Observations on hospitalized patients with haemorrhagic fever. Am J Trop Med Hyg; 18: 954–71.

Pasha O (2005). Viral Hemorrhagic fever in Karachi 2005 Infect Dis J;14:133-4.

Simon F, Javelle E, Oliver M, Leparc-Goffart I, Marimoutou C (2011). Chikungunya virus infection. Curr Infect Dis Rep; 13 :218-28.

Staikowsky F, Talarim F, Grivard P, Souab A, Schuffenecker I, LeRoux K, et al., (Provide names of other authors) (2009). Prospective study of chikungunya virus acute infection in the Island of La Reunion during the 2005–2006 outbreak. *PLoS ONE;4:* e7603.

Staples JE, Breiman RF, Powers AM (2009). Chikungunya fever: An epidemiological review of a re-emerging infectious disease. Clinical Infectious Diseases; 49:942–8

Thiberville SD, Boisson V, Gaudart J, Simon F, Flahault A, Flahault A et al., (Provide names of other authors) (2013). Chikungunya fever: A clinical and virological investigation of outpatients on Reunion Island, South-West Indian Ocean. PLoS Negl Trop Dis; 7: e2004.

World Health Organization (WHO) (2006). Chikungunya in India. http://www.who.int/csr/don/2006_10_17/en/

World Health Organization (WHO) (2012). Proposed case definition of chikungunya fever (WHO, SEARO). http://www.searo.who.int/entity/emerging_diseases/topics/Def_Chikungunya_Fever.pdf

World Health Organization(WHO)(2011). Comprehensive guidelines for prevention and control of dengue and dengue haemorrhagic fever. http://www.searo.who.int/entity/vector_borne_tropical_diseases/documents/SEAROTPS60/en/index.html