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Clinical presentation, neurological manifestations and correlation of laboratory parameters among patients of chickungunya fever presenting in a tertiary care setting, Pune, India

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Abstract
Chikungunya (CHICK) fever is an acute febrile illness associated with severe, often debilitating polyarthralgias. Because of dearth of information on CHIK fever, its clinical presentation and significance of laboratory testing in the diagnosis of CHIK fever in Indian population, this study was planned. This was an observational, prospective epidemiological study conducted on Indian patients visiting Rao Nursing Home, Pune and confirmed/ suspected of suffering from CHICK fever. From October to November 2016, total 232 patients were enrolled in the study. Of the 232 samples tested for CHICV IgM antibodies, 51(21.98%) were positive (confirmed) cases. Fever was a presenting symptom in all cases, arthralgia was present in 46 (90.20%) confirmed cases and 146(80.66%) suspected cases. Neurological manifestation was seen in 9 (17.65%) confirmed cases. Mortality was recorded in 3 (5.88%) confirmed cases. Further studies need to carried out to find out if neurological complications in CHICV is associated with increased mortality.

Keywords: chikungunya virus, CHICV IgM antibodies, dengue virus (DENV), mono infection, dual infection

Introduction
Chikungunya (CHICK) was first detected in 1952 in Makonde, United Republic of Tanzania and derives its name from *kungunyala*, the Swahili word for the contorted posture of patients because of their arthritic symptoms. It was first described by Robinson and Lumsden in 1953 [1]. Epidemics were subsequently noted in the Philippines (1954, 1956 and 1968), Thailand, Cambodia, Vietnam, India, Myanmar and Sri Lanka [2]. In India, major epidemics of chikungunya were reported in 1963 in Kolkata, in 1965 in Puducherry (formerly Pondicherry), Tamil Nadu, Andhra Pradesh, Madhya Pradesh and Maharashtra and again in 1973 in Maharashtra [3]. Thereafter, sporadic cases continued to be recorded in Maharashtra during 1983 and 2000 [4]. Since 2003, there has been a resurgence of chikungunya outbreaks in the islands of the Pacific Ocean, including Madagascar, the Comoros, Mauritius and Reunion Island [5]. In January 2006, there was a very large epidemic in Reunion Island followed quickly by the one in India [6]. Almost 1.3 million suspected chikungunya fever cases were reported in India [7].
Resurgence of chikungunya has been attributed to various factors including globalization, increase in the mosquito population, loss of herd immunity and the mutation A226V in the E1 gene causing a significant increase in CHIKV infectivity for *Ae. Albopictus* [5]. India reported 1.3 million cases in 2006 but no data on mortality were available except for two reports – one on a subset of patients and one deductive. In one report, among 90 laboratory-confirmed chikungunya cases hospitalized in Ahmadabad, 18 deaths were recorded of which 15 were aged 60 years or older and five had co-morbidities [8]. The other report was deductive; based on death records during previous years in Ahmadabad, the excess deaths that occurred during the outbreak period was attributed to CHIKV and a mortality rate of 4.9% was reported [9].
Because of dearth of information on CHIK fever, its clinical presentation, atypical manifestations and significance of laboratory testing in the diagnosis of CHIK fever in Indian patients, this study was planned. Objective of this study was to assess the epidemiology pattern, the common clinical presentation and complications of CHIK fever, and correlation of symptoms with positive laboratory testing in clinically suspected and confirmed Indian patients of CHICK fever. In this paper, we have also discussed the priorities for further studies needed for effective disease control and prevention.

Materials and Methods
This was an observational, prospective epidemiological study done in Indian patients. The study was approved by the Institutional Ethics Committee. In this descriptive study, a total of 232 suspected cases of chickungunya fever during an epidemic in Pune from October 2016 to November 2016 were enrolled consecutively. These patients visited General Medicine OPD (Outdoor) or were admitted in the wards (Indoor) at Rao Nursing Home, Pune. During this period, subjects having clinical triad of fever, arthralgia (joint pain) and rashes or presence of any two of the above three clinical features suggestive of chikungunya fever were included in the study for screening. Those fitting into the inclusion and exclusion criteria were enrolled in the study. After obtaining the informed consent form, each patient was assigned a unique identification number.

The Case definitions used in the study [10]
- ***Suspected case*** **-** An acute illness characterized by sudden

onset of fever with one or many of the following symptoms: joint pain, headache, backache, photophobia, arthralgia, rashes, etc.

- ***Probable case*** **-** Above features and positive serology when single serum sample was taken either in acute onset phase or during the convalescence.
- ***Confirmed case*** **-** A confirmation was done by one of the following methods:
  1) Four-fold haemagglutination inhibition (HI) antibody difference in paired sera.
  2) Detection of IgM antibodies against chikungunya virus (CHIKV IgM).
  3) Virus isolation from serum/body fluid.
  4) Detection of chikungunya virus nucleic acid in sera by RT-PCR.

Detailed history was taken and clinical examination was carried out of all cases. Information on patient's demographic characteristics and clinical presentations was entered in to the Case Report Form (CRF). The detailed examination also included looking for rash, lymphadenopathy and joint affection. Pain scale of patients with joint involvement was recorded using Visual Analog Scale (VAS) which scored pain from 0-10. Restriction of joint movement of involved joints, bleeding tendency was also recorded. The detailed systemic examination of the Cardiovascular, Respiratory, Abdominal and Central nervous system was done. Arterial blood (8-10 ml) was withdrawn from the patients using standard aspetic precautions. Routine investigations (total leucocytes count, differential leucocytes count, platelets count, liver function test, kidney function test) were done and detection of CHIKV IgM antibodies in serum by ELISA method was carried out in all subjects. Also, the serum was tested for malarial parasite using malaria rapid test (Qualitative detection of malaria parasites P. falciparum, P. vivax antigens in human blood), for Typhus fever using Weil felix serine antigen kit, for Dengue using ELISA for detection of NS1 and IgM DENV, for Typhoid using Widal tube agglutination test, for Leptospirosis using Leptospira IgM and IgG rapid diagnostic card test. These tests were done in the Pathology and Microbiology Department of Rao Nursing Home. Additional test carried out in patients included blood culture, CSF routine examinations and culture as indicated in the cases. In patients presenting with neurological manifestations, EEG and CT scan was also performed.

Results and Discussion

From October 2016 to November 2016, total 232 patients suspected or confirmed CHICK fever were enrolled in the study. Out of 232 patients, 181 patients were suspected of CHICK fever and 51 patients were seropositive confirmed cases. Hospitalisation was required for 189 (81.47%) cases and 43(18.53%) cases were treated on OPD basis. Out of 189 hospitalized patients, 85.18% of patients required admission in Intensive Care Unit and 14.81% were admitted in wards. Average length of stay ranged from 3 to 20 days for hospitalized cases. More cases (51.75%) were recorded in the month of November 2016. (Table 1)

Table 1: Reported period of suspected/confirmed chikungunya cases

Month	Outdoor cases	Indoor cases	Total (%)
Oct	21	91	112 (48.28)
Nov	22	98	120 (51.72)
Total	43	189	232 (100%)

Mean age of confirmed CHICK fever cases was 54±19.57 years (range 17 to 87 years). Mean age of suspected CHICK fever cases was 45.95years (range 13 to 88 years). The age distribution of confirmed and suspected case is shown in Table 2. Male to female ratio was nearly 1:1 (25 males, 26 females) in confirmed cases and 1.26:1 in suspected cases.

Table 2: Age distribution of chikungunya cases

Age (Years)	Confirmed (n=51) (%)	Suspected (n=181) (%)
17 to 39	17.65	44.20
40 to 59	39.22	33.15
60 to 90	43.14	22.65

Clinical profile of chickungunya confirmed and suspected cases is shown in Table 3.The most common presentation in confirmed and suspected cases was fever (100% and 97.79%), joint pain(90.2% and 80.66%), rash (45.1% and 50.28%) respectively. The classical triad of fever, joint pain and rash was seen in 43.14% confirmed cases and 41.44% suspected cases. Headache was present in 17 (33.33%) confirmed cases out of which (55.55%) had neurological manifestations.

Table 3: Clinical profile of Chikungunya cases

Clinical Presentation	No of Confirmed cases (n=51) (%)	No of Suspected cases (n=181) (%)
Fever	100	97.79
Joint pain	90.20	80.66
Rash	45.10	50.28
Fever + Joint pain + Rash	43.14	41.44
Headache	33.33	39.78
Oral ulcer/Apthous ulcer	00.00	00.00
Lymph node enlargement	00.00	3.87
Haemorrhagic manifestations	00.00	00.00
Neurological manifestations	17.65	00.00

Overall, rashes were generalized, erythematous, nonpruritic and maculopapular. Apthous ulcers or oral mucosal lesions were not recorded in any case. Joint involvement included predominant involvement of small joints. Large joints were also involved in some patients. The joints involved included small joints of the hand (26.29%), wrist (28.44%), ankle (18.96%), elbow (13.79%) and knee (12.50%). Restriction of joint movement was observed in 8.85% cases and the pain scale recorded on VAS was from 6-10 in cases with joint involvement.

Neurological manifestations was seen in 9 (17.65%) cases, all of which were confirmed cases. As shown in Table 4, patients with neurological manifestation presented with altered sensorium (77.78%) and seizures 22.22%. Viral encephalitis was the presentation in all cases. Overall, 5.88% patients confirmed with CHICKV died and all these patients had neurological manifestations. Mortality cases had an age range from 18-81 years with an average age of 46 years with male to female ratio of 1:2. One case of CHICV infection in whom mortality was recorded had co- morbid conditions such as diabetes and hypothyroidism. However, the associated illness did not contribute to the outcome. CT scan was performed in all cases with neurological manifestations and was normal in 5 (55.56%) cases, while age related cerebral atrophy was seen in 4 (44.44%) cases. CSF studies performed in all cases with neurological manifestation was normal and there was no evidence of meningitis. Nerve Conduction Velocity studies performed in all cases were normal and there was no evidence of neuropathy. Hemorrhagic manifestations were not reported in any suspected or confirmed cases.

Table 4: Clinical presentation of CHICV Patients with Neurological manifestations

Clinical Symptoms	Percentage (n=9)
Altered Sensorium	77.78
Seizures	22.22
Normal CT Scan	55.56
Age related Ccerebral atropy	44.44
CSF examination - elevated protein	77.77

Laboratory investigations revealed leukopenia with WBC count less than 4000/cumm in 18 (35.29%) confirmed cases (Table 5). Thrombocytopenia with platelet count less than 50,000 lakhs/cu.mm was present in 6 (11.76%) confirmed cases. Platelet count ranged from 10,000 to 2,50,000 lacs/cu.mm. Some patients also had deranged liver function test and renal function test. CHICV IgM ELISA was positive in cases where the mean duration symptoms was 14.09 days (Table 6). Dual infection was seen in 4 (7.84%) cases with DENV and CHICV. In cases with dual infection, neurological manifestation was seen in 1(25%) case and mortality was recorded in 1(25%) case. All the cases (n=232) were followed up during the course of hospital stay for indoor patients and outdoor patients during their subsequent visits after discharge which was after 7 days. 92 (47.91%) cases who had joint involvement recovered with decreased swelling and improvement was observed in range of movement of the involved joints.

Table 5: Laboratory investigations in CHICV cases

Laboratory investigations	No. of confirmed cases (n= 51) (%)	No. of suspected cases (n= 181) (%)
Leukopenia <4000	35.29	6.08
Platelet count <50000	11.76	4.97
Deranged serum bilirubin levels	7.84	3.31
Deranged serum glutamic oxaloacetic transaminase (SGOT)	19.61	9.94
Deranged serum glutamic pyruvic transaminase (SGPT)	21.57	18.23
Deranged blood urea level	5.88	2.21
Deranged serum creatinine	5.88	4.42
Dengue ELISA positive	7.84	0.00
Malarial parasite positive	0.00	0.00
Widal test positive	0.00	0.00
S. Leptospira positive	0.00	0.00

Table 6: CHICVIgM antibodies positivity and co-relation with onset of diseases

CHICV IgM ELISA	Onset of symptoms (Mean) days	Standard Deviation
Positive >9	14.09	4.88
Negative <9	3.26	4.09

Chickungunya confirmed cases recorded in Pune city as per statistics of Pune Municipal Corporation during the months of October and November 2016 was 1744 in comparison to 18 confirmed cases recorded in 2015 during the same period. Pune constituted 92% of the total cases recorded in Maharashtra during this outbreak. In the present study, seropositivity was 21.28 percent, where 51 of the suspected cases were IgM antibody positive out of 232 tested samples. A multicentric hospital based trial conducted in India recorded a seropositivity of 25.37 percent cases [11].

Average age recorded in the study was 54 years, in comparison to other studies where the age recorded was14-44 years and had a predominant female affection [12]. The maximum cases were reported in November and the average length of stay ranged from 3-20 days. Similar data was recorded in a study carried out in patients in a tertiary care centre Nagpur, Maharashtra, India [13]. Dual infection with CHICKV and DENV IgM antibodies was recorded in 7.84% of cases in the present study as compared to 9.5% dual infection cases recorded in patients with acute febrile illness attending a tertiary care hospital in Mumbai [14]. Co-infected or dual infection cases have higher mortality (25 % vs. 5.88%) than mono infected cases. The mortality rate recorded in 2015 in a study conducted in Pune was 12% in cases of dual infection in comparison to 2% with mono infection [15]. Neurological complications was seen in 17.65% confirmed CHICV cases. Neurological complications was reported 16.3% in a study carried out in 2006 in Nagpur, India during the epidemic of chikungunya [16]. The most common neurological manifestation was encephalitis and all the cases presented with neurological symptoms at the time of hospitalisation. The duration of onset of symptoms ranged from 13-19 days.

Limitations of study

The limiting factor of our study could be unavailability of RT-PCR diagnostic test in our institution because it is not a standard of care. Studies using IgM antibodies to Chikungunya & Dengue for diagnosis of Dengue and Chikungunya co-infection have been conducted earlier [17]. Suspected cases follow up titers of CHICV IgM levels was not carried out who were negative on initial testing. RT-PCR studies of CSF of cases presenting with neurological manifestations could not be carried out at the study center.

Conclusion

Thus, the most common presentation of CHICK fever in confirmed cases was fever, joint pain and rash, with classical triad of fever, joint pain and rash seen in majority of patients. Neurological manifestations of CHICK fever is also rising. CHICV infection are re-emerging and are associated with increasing mortality especially when associated with neurological manifestation. Dual infection with Dengue virus increases the mortality chances in patients with CHICV infection. Although**,** chikungunya fever is self-limiting; the morbidity can be very high in major outbreaks, resulting in a heavy social and economic toll. The prevention of the disease requires a planned approach, besides knowledge and awareness on the early warning signs. An integrated vector management through the elimination of the breeding sites, the use of anti-adult and anti-larval measures and personal protection will contribute to the prevention of out- breaks. A community empowerment and mobilization is crucial for the prevention and control of Chikungunya. Further studies to evaluate and identify the risk factors associated with increased mortality of Chickungunya are required.

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