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Clinical complications of Chikungunya fever in Mauritius

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ABSTRACT: Chikungunya fever, an emerging mosquito-borne viral disease, has affected Mauritius with two recent outbreaks in 2005 and 2006 respectively. A study was carried out in 2007 to describe the clinical complications post-Chikungunya infection. Ethical clearance was obtained for this study. Data collection was carried out in February and March 2007 on a sample of people who had suffered from Chikungunya fever by means of a comprehensive questionnaire. Participants comprised 77 people; there were 41 males and 36 females. Participants ranged from 6 to 69 years. 70 participants experienced persisting joint pains for at least 6 months following the acute phase. Of these, 35 had residual joint complaints after 6 months. 44 participants suffered from psychological sequelae. 10 participants had dermatological sequelae, 6 had iatrogenic complications due to non-steroidal anti-inflammatory drug (NSAID)-induced gastritis, and 3 participants with serologically confirmed Chikungunya fever had neurological manifestations and changes on CT/MRI which could correspond to demyelination. Statistical analysis demonstrated that there was a weak linear relationship between the number of complications and increasing age; there was a significant difference in the number of complications according to gender, females being more affected than males; participants with co-morbidities had more complications and psychological sequelae than previously healthy participants. This study highlights that Chikungunya fever, which causes a significant impact on health in the acute phase, can have significant sequelae months afterwards and this includes psychological sequelae.

KEY WORDS: Chikungunya fever; Complications; Residual joint symptoms; Psychological sequelae

INTRODUCTION

The island of Mauritius in the Indian Ocean (population 1.2 million) first encountered Chikungunya virus (CHIKV) in early 2005 with a localized outbreak (about 3600 inhabitants affected in the capital city mostly) and a major island-wide outbreak occurred in February/March 2006 (about 11000 inhabitants affected).[1] CHIKV, an alphavirus of the family of Togaviridae was first isolated in Tanzania in

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1953[2] and has been spreading to different parts of the world. In 2004, an epidemic believed to originate from coastal Kenyan towns spread to the Indian Ocean islands of Comoros, Reunion, Mayotte and Mauritius.[1] Since, there have been epidemics in India, the Maldives, Gabon, Italy (Ravenna province) and Singapore.

The disease is generally believed to be a mild self-limiting illness characterized by an incubation period of 4-5 days followed by fever and joint symptoms. A recent outbreak in Mauritius showed that important clinical manifestations included fever, joint pain, joint swelling, chills, headaches and rash in the acute phase of the illness. Subsequent to recent outbreaks in other countries, severe clinical manifestations other than joint complaints have been reported: neurological complications[3-6], liver involvement[4,5], multiorgan failure[5] and severe dermatological complications[4]. Iatrogenic complications have also been observed[4,7,8]. An excess mortality has been noted during CHIKV outbreaks and reported in several studies[9-11]. Direct and indirect complications related to CHIKV have also been observed mainly in the elderly, in people with chronic diseases, during pregnancy and in neonates. Residual and chronic symptoms have also been documented [3,4,7].

In this study the complications and sequelae of CHIKV were explored in a sample of people affected in Mauritius following the two outbreaks.

METHODOLOGY

Ethical clearance for this retrospective study was obtained from the Ministry of Health and Quality of Life (Research protocol number: MHS 458/95). Data collection was carried out in February and March 2007 on a sample of people who had suffered from CHIKV infection in either the 2005 or 2006 outbreaks and diagnosed according to clinical and epidemiological criteria at the time i.e. a person was considered as suffering from chikungunya fever if he had a sudden onset of high grade fever, polyarthritis and maculopapular rash. Participants were recruited randomly from the community and from referral from medical practitioners and specialists. Inclusion criteria were past CHIKV infection and willingness to participate in the study. Participants younger than 18 years were interviewed in the presence of parents, and with parental consent.

Medical practitioners who had treated patients with CHIKV were interviewed prior to questionnaire design. Complications noted in literature review were included in the questionnaire. Data was collected by means of a comprehensive questionnaire which included a section on personal and socioeconomic data, details of the CHIKV infection and its duration, acute manifestations of the disease, complications following the infection, iatrogenic complications, residual symptoms and psychological sequelae. The questionnaire consisted mainly of closed-ended questions for greater precision, uniformity and easier analysis and covered body systems and known Chikungunya complications in a systematic way. The same interviewer administered the questionnaire to ensure accuracy and to minimize interviewer bias. Although participants were recruited from all ethnic groups, complications were not analyzed according to ethnic group in this study.

For statistical analysis, SPSS 11.0 was used. Statistical tests used were the student's t-test, the chi-squared test, and Pearson correlation coefficient. 95% confidence interval was used for all tests. Results were considered as statistically significant at a p-value of < 0.05.

RESULTS

There were 77 participants in the study: 41 males (53%) and 36 females (47%). The age distribution was as follows: 0-10 years (3%), 11-20 years (3%), 21-30 years (17%), 31-40 years (14%), 41-50 years (25%), 51-60 years (29%), and 61-70 years (9%). 26% of participants in this sample had a co-morbidity or underlying chronic disease such as diabetes mellitus, hypertension or rheumatoid arthritis.

Duration of the acute phase of the illness was as follows: 3-5 days (42%), 6-7 days (27%), 10-15 days (22%), and more than 15 days (9%).

Medications used during the acute phase were as follows: NSAIDs (88%), paracetamol (88%), antibiotics (12%), chloroquine (1%) and others (21%). In the majority of cases, medications were taken in combination. 21% of the participants who had been prescribed "other" drugs were not aware of the nature of the medications prescribed to them.

After the acute phase of Chikungunya infection, participants complained of joint, psychological, dermatological, iatrogenic and neurological complications as described in **Table 1**. The distribution of the different complications showed a higher frequency in females than in males (**Table 1**).

Table 1: Distribution of complications post-CHIKV in sample and by gender

Distribution of Complications	Number	Males	Females
Joint	70	34	36
Psychological	44	19	25
Dermatological	10	4	6
Drug-induced	6	2	4
Neurological	3	1	2

Joint complications

After the incapacitating arthralgia of the acute phase, 70 participants (92%) complained of persisting joint symptoms which consisted mostly of arthralgia, stiffness in the joints and joint swelling. Thirty-five participants still had residual joint pain or stiffness at least 6 months after the onset of the infection.

The most affected joints in the chronic phase were the interphalangeal joints, the wrist joint and the ankle joint. Four patients also complained of persistent shoulder pain. Pain in the sole or in the heel of the foot was experienced in some patients. One patient experienced a burning sensation in the heel of the foot at rest. Joint stiffness affected mainly interphalangeal, wrist, knee and ankle joints. Persistent joint swelling involved mainly the ankle joints, followed by the interphalangeal and knee joints. However the swelling gradually resolved over several months. Other residual joint manifestations were mild joint deformities and pigmentation over small joints mainly.

Neurological complications

Three participants in this study presented with neurological symptoms after having had CHIKV infection. They had had no neurological complaints previously. In these patients, IgG antibodies against CHIKV were demonstrated by complement fixation test at the time of interview a year after the initial infection. Details of these three cases are as follows:

Case 1: A 48-year old female patient with a past history of hypertension presented with a 5-month history of severe headaches, numbness and tingling of extremities since the CHIKV infection. A CT scan was done.

Case 2: A 55-year old male patient with a past history of diabetes presented with severe headache some days following the CHIKV infection. The patient had an MRI scan performed.

Case 3: A 58-year old female patient, with a past history of diabetes and recently diagnosed hypertension presented with severe headaches, tingling, drowsiness, stiff neck, and vertigo some days following CHIKV infection. A CT scan and an MRI scan were both carried out in this patient.

In all cases, there were radiological changes on the scans, which could correspond to demyelination.

Other cases with neurological symptoms that did not have further neurological investigations were as follows: a participant with no previous neurological history experienced persistent neck stiffness and pain. Another participant complained of frequent headaches, neck stiffness and recurrent neck lymphadenopathy for a year after the CHIKV infection. A participant had backache, neck stiffness, and tingling in the hands and legs lasting for a month after the infection. Another case involved a participant with no underlying conditions who complained of persistent numbness, tingling, tremors, stiff neck, vertigo, drowsiness and confusion after CHIKV infection. One participant complained of persisting numbness in the fingertips. Another diabetic and hypertensive participant also experienced numbness and tingling in the hands. There were several complaints of increased frequency of headaches after the infection. In addition, two cases of increased somnolence were also noted in participants after CHIKV infection.

Dermatological complications

A skin rash was noted in most patients during the acute phase which resolved in most cases. However, 10 participants had dermatological sequelae consisting mainly of pigmentation which were either facial (nose and central area of the face) or on limb extremities or over joints which were gradually fading.
In one participant who had underlying diabetes, a vesicular fluid filled rash was noted in the acute phase. Another elderly female patient with underlying diabetes and hypertension complained of persistent rash and pruritus over the arms, legs and neck after the CHIKV infection. There were also two complaints of diffuse hair loss, which was noted after the CHIKV infection.

Iatrogenic complications

Six participants had iatrogenic complications due to gastritis induced by NSAIDS out of 68 participants who had been prescribed this drug.

Psychological complaints

Forty-four (57%) participants suffered from psychological complaints in the chronic phase. These complaints included insomnia, aggressiveness, pessimism, lack of concentration, depression, and confusion. The distribution of psychological complaints in males and females is shown in **Table 2**.

Association of complications with age, gender and co-morbidity

Analysis was done to find out whether there was a correlation in the number of complications with age. A linear regression was done and the r-value obtained was 0.237 (Pearson's correlation coefficient). So, one can conclude that there was a weak correlation between these two variables indicating that the number of complications increased with age. A student's t test was done to investigate whether the number of complications differed in male and female participants. This test demonstrated that there was a significant difference in the number of complications according to gender at a p-value of 0.001 with females being more affected than males. Participants with co-morbidities had more complications post-CHIKV infection than previously fit participants. This was deduced by the student's t test at $p<0.05$. Participants with co-morbidities also had more psychological sequelae than previously fit participants. This was deduced by the chi-squared test at $p<0.05$.

Table 2: Distribution of psychological complaints post-CHIKV in sample and by gender

Distribution of psychological complaints	Number	Males	Females
Pessimism	37	16	21
Lack of concentration	35	16	19
Insomnia	31	12	19
Depression	31	13	18
Aggressiveness	22	8	14
Confusion	17	9	8

DISCUSSION

This study contributes in informing further about the complications of Chikungunya fever in Mauritius despite the limitations of small sample size and lack of serological data. However, although the participants did not have a laboratory-confirmed diagnosis of past CHIKV infection, they had all been diagnosed clinically during the outbreaks according to clinical and

epidemiological criteria at the time. In addition, there were no other concurrent infections prevailing at the time which would have caused diagnostic confusion.

The questionnaire was designed so that it would be simple to administer, valid and reliable and interviewer bias was minimized by having the same interviewer carry out all the interviews. However since this was a retrospective study, it is possible that recall of all symptoms and complications might not be complete and exact. This is a limiting factor in this study. Another limiting factor is that those people who chose to participate in this study may have had more complications than those who did not. Nevertheless this exploratory study gives a useful picture of complications post CHIKV in Mauritius.

Ninety-two percent of participants complained of joint symptoms as compared to 73-80% prevalence of joint complications in Reunion in serologically proven cases.[4] The most common joint symptoms were arthralgia, stiffness, and swelling over three weeks to one year after the infection. This is similar to findings by **Kennedy et al**[12] who described articular pain, tenderness and swelling in 20 patients four to six months post-CHIKV. The most affected joints in the longer term in our study were the interphalangeal joints, the wrist joint, the knee joint and the ankle joint, and also in some cases the shoulder joint. There have been varying reports about which joints are most affected post-CHIKV; **Clarris**[13] has reported that the knees, ankles, shoulders and fingers to be most affected whilst **Boutin**[7] has reported that the small joints were the most affected.

The three neurological cases described in our study are highly suggestive of neurological complications following infection with CHIKV. Other studies have also described meningitis and encephalitis[14] and adult cases of meningoencephalitis have been diagnosed both clinically and radiologically in serologically proven Chikungunya cases.[3] There have also been cases of meningoencephalitis in neonates, Guillain Barré syndrome and other cases of CNS involvement.[4] Thus our study also indicates that CHIKV may be neurotropic as are other viruses from the Togaviridae family.[3]

About 13% of our sample had dermatological involvement in the longer term. The eruption of a fluid-filled vesicular rash in a diabetic patient, who needed hospitalization, appeared similar to the six severe dermatological cases found in Reunion[5], which has the same hyper endemic situation of diabetes as Mauritius.

Psychological aspects of CHIKV have been not been reported previously. Many viral infections are known to be associated with symptoms such as lassitude, fatigue and depression requiring a long period of recovery. It appears from our study that CHIKV also has a significant psychological burden. Studies have also shown that many infectious and non-infectious diseases are associated with immune activation and the production of cytokines in the brain. These cytokines within the brain induce a depression-like behavioral syndrome.[15] These may partly explain the psychological complaints following CHIKV. However this aspect of complications following CHIKV needs further investigation by the follow-up and investigation of affected people.

It was shown statistically that there was a weak linear relationship between increasing age and the number of complications post-CHIKV. **Paquet et al**[3] have described indirect consequences of CHIKV in debilitated and weak patients such as the elderly and those with underlying chronic diseases. Neurological forms of the disease have also been confirmed in elderly patients already vulnerable due to old age or underlying chronic diseases.[3] It was also shown statistically that the number of complications is increased in people with underlying chronic diseases or any other co-morbidity. It is plausible such people have a depressed immune status and are thus more prone to complications. Statistical analysis has also shown that the number of complications in females is greater than in males. This finding is interesting and the gender difference noted in this study needs to be confirmed in larger studies. Possibly this gender difference may reflect underlying differences in the immune responses of males and females.

CONCLUSION

This study highlights that CHIKV which causes a self-limiting disease involving mainly joint symptoms in the acute phase, can have important sequelae including significant psychological sequelae months afterwards.

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