Post-Chikungunya Chronic Arthritis – Our Experience with DMARDs Over Two Year Follow Up

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Abstract
Aim: 1) To study clinical features and laboratory findings in patients of post chikungunya chronic arthritis (PCCA). 2) To study effectivity of disease modifying antirheumatic drugs (DMARDs) in treatment of post-chikungunya chronic arthritis.

Materials and Methods: Sixteen Chikungunya IgM positive patients having arthritis lasting more than 3 months in spite of NSAIDs and Hydroxychloroquine therapy were selected. Their clinical, laboratory and radiological features were noted. Disease activity was assessed by clinical parameters and Disease Activity Score System (DAS 28). Functional status was assessed by HAQ Questionnaire on follow-up visits over next 2 years. Effectivity of treatment with Sulfasalazine and Methotrexate was assessed.

Results: Chronic inflammatory polyarthritis does occur following chikungunya infection. It involves large and small joints of hands and feet and is erosive and deforming. It is rheumatoid factor negative. AnticCP antibody was positive in majority. Synovial biopsy revealed non-granulomatous chronic synovitis with infiltration with lymphocytes and plasma cells. It was negative for chikunguya RNA. Treatment with Sulfasalazine with and without methotrexate produced good response in 71.4% and 12.5% respectively.

Conclusions: Chronic inflammatory, erosive and rarely deforming polyarthritis does occur after acute chikungunya infection in some (5.6%). It is seronegative and AntiCCP positive in majority. DMARDs like sulfasalazine and methotrexate are required and effective in treatment of PCCA.

Introduction
Chikungunya (CHIK), an alpha viral disease caused large epidemic in India in 2006. Though generally described as self-limiting disease, prolonged arthralgias (12-13%) rarely destructive arthropathy is reported after CHIK. We witnessed both acute and chronic arthritis following CHIK during this period that did not respond to the treatment described in earlier literature. Review of literature does not reveal much information on clinical, laboratory features or management of post CHIK chronic arthritis (PCCA) except a pilot study stating effectivity of chloroquine phosphate in CHIK arthritis for symptom relief. One Indian study is available recently on use of Hydroxychloroquine and methotrexate in chronic CHIK arthritis. It has its limitations as there was no virology confirmation of the cases. Hence we took up this study to know the clinical features of PCCA and effects of various disease modifying antirheumatic drugs.

Aims and Objectives
This study on chikungunya follow up aims to know the 1) clinical profile and laboratory features of patients presenting with chronic arthritis and 2) To study the effects of Disease modifying anti rheumatic drugs (DMARDS) on post CHIK chronic arthritis.

Selection Criteria
Exclusion criteria were 1) Patients having preexisting arthritis. 2) Patients having similar looking illnesses (diagnosed by doing appropriate tests).

Materials and Methods
The study was carried out at MIMSR Medical college and Hospital, Latur and Sanjeevan hospital Latur, between Dec 2006 – Dec 2008. Ethics committee approval and written informed consent of all patients was taken. We followed up 625 patients of acute CHIK (diagnosed clinically) during the epidemic. Inclusion criteria for the present study were as follows – 1) Patients having chronic arthritis (defined as arthritis lasting beyond 3 months from acute attack), 2) Presence of anti CHIK IgM antibody. Thirty seven (5.9%) developed chronic arthritis with objective evidence of synovitis. Patients with only arthralgias were not included. All of them had received treatment with NSAIDs and Hydroxychloroquine. All were subjected for CHIK IgM testing (NIV, Pune and Ranbaxy lab.). 16 patients fulfilling selection criteria were included.

Demographic details, past and present history including details of treatment were recorded in all. Baseline clinical features and parameters for disease activity including tender joint count (TJC 0-28), swollen joint count (SJC), ESR, duration of morning stiffness (in minutes) were recorded. Functional status was assessed by HAQ questionnaire. Baseline laboratory workup in the form of CBC, ESR, CRP (normal <.6 mg/dl), urine examination, R Factor (RF) with titer (turbidimetric immunoassay), AntiCCP antibodies (enzyme immunoassay, Ranbaxy lab.) was done in all. Tests like ANA and serum Uric acid were done to rule out similar looking illnesses. X ray of hands was done in all patients during first visit and 1 year after their inclusion in the study. Three patients were subjected for MRI scan of the most affected joints. Histopathology and RT - PCR (Reverse transcription polymerase chain reaction) for viral study was done on synovial biopsy obtained from knee joint of one patient.

Patients were first reviewed 6 weeks after enrolment and were followed up every 2 monthly till Dec 2008 (Mean 18 months) Follow-up included clinical examination(including 4 monthly fundus examination) and lab investigations (CBC, LFT, KFT, urine examination) for drug side effects. Disease assessment was done at baseline, at 3 and 6 months, 1yr and at the end of 2years. Disease activity was assessed on the basis of TJC (0-28), SJC, ESR, duration of morning stiffness and functional status was...
assessed by HAQ questionnaire. Disease Activity Score (DAS) was calculated (Inactive disease – DAS < 3.2, Moderately active disease- DAS 3.2 to 5.1 and Active disease – DAS >5.1). Treatment response was defined as poor if change in DAS < 0.6., Moderate if change in DAS 0.6-1.2. and good response if change in DAS >1.2. Statistical analysis was done using mean, median, percentages and standard deviations. We applied paired t test for initial stage and at two year follow up. Probability was calculated at 95 % confidence interval and p< 0.05 was considered significant. We used Statsdirect 7.2.0 and Excel 2003 software for calculation.

### Treatment

1) All patients received NSAIDs (Tab Etoricoxib 90 mg /day or Aceclofenac 100 mg bid) for initial two weeks and as and when required afterwards for symptom relief. 2) Steroids (Tab. Prednisolone 5-10mg /day) were given to all patients for initial period of 2 - 4 wks and stopped later on. 3) All patients were started initially on combination therapy of Sulfasalazine (SSZ 1-2 gms / day in gradually increasing and divided doses) and Hydroxychloroquine (HCQ 200 mg / day). Those having good response were continued on the same drugs 4) Methotrexate (MTX) was added to the regimen in those having poor to moderate response to HCQ and SSZ combination therapy after 3 months. All the patients continued therapy till the end of study period.

### Results

We studied total 16 patients between Dec 2006- Dec 2008 with M: F - 7:9. Their age ranged from 23 yrs to 75 years (mean 50.93yrs). Multiple family members were affected during acute phase in 15/16 (93.7%).

Clinical features - All patients had chronic symmetric polyarthritis with morning stiffness (mean duration 90 min). Most commonly affected joints were wrists, MCPs, PIPs, elbows, shoulders, knees, ankles and MTPs. (Fig -1) DIP joints were involved in 12.5%. Temporomandibular (TM), sternoclavicular, sacroiliac joints (SI) and spine involvement was not seen in this series. Joints were warm and tender. Synovitis with or without effusions was seen in all. Tenosynovitis, bursitis (retrocalcaneal) were noted. Flexion deformity of hands occurred in 1 patient. Fatigability and soft tissue pain (intermittent, lancinating) in arms, forearms, thighs and forefeet was seen in all. Edema of hands and feet mimicking RS3PE (Remitting seronegative symmetric synovitis with pitting edema) like picture was noted in 4(25 %) patients (Fig. 2). It was unilateral in one patient. One patient had diabetes mellitus with hypertension as co morbid condition.

### Laboratory Features

CBC revealed normal Hb in 11 (68.75 %) and low Hb in 5 (31.25%) patients, normal TLC and DLC in all. Platelets were normal in all except 2, where thrombocytosis was noted. CRP was raised in 11 (68.75%) and normal in 5 (31.25%). ESR was raised in all patients (Mean 47 mm /1 hr.) Urine examination was normal in 14/16(87.5 %) patients, trace albuminuria in 2/16 (12.50 %). Sr. Uric acid, LFT, KFT and ANA done at baseline were normal in all.

RF and anti CCP antibodies were done in all. Out of 16 patients 2 were positive for RF (12.5%) and 9 were positive for antiCCP (56.5 %). One (6.25 %) was positive for both antibodies while six (37.5 %) were negative for both the antibodies. Out of 14 patients who were RF negative, 8 were anti CCP positive and out of 7 who were anti CCP negative, one was RF positive.

X-Rays of hands and other affected joints revealed reduced joint space and periarticular osteopenia. Erosions developed in 5/16 patients. (31.25%). MRI of joints was done in three patients. Knee joint MRI showed synovial thickening, suprapatellar pouch effusion, Baker’s cyst (Fig. 3) and marrow edema. Marginal erosions in medial and lateral condyles of femur and in patella were seen (Fig. 4). Hand MRI showed small periarticular erosions in phalanges, metacarpals and carpals. One patient had lack of erosions on MRI. Synovial biopsy revealed hyperplastic synovial tissue with extreme passive congestion and fibrinous exudates. There was dense mixed lymphocytic and plasma infiltrate with few PMNs. Sub epithelial lymphoid follicular aggregates amidst mixed inflammatory infiltrate, congested blood vessels and proliferating fibroblasts were seen (Fig. 5) Perisynovial fat showed focal lymphocytic and plasma cell infiltrate mixed
presents in 2 stages, an initial abrupt onset severe polyarthritis with or without rash, followed by disabling peripheral rheumatism.6 Arthritis in acute phase involves small and large joints of hands and feet.12-13 % cases develop chronic arthritic illness7 and rarely destructive arthropathy. Considering the size of affected population in India this amounts to a huge number. In this study, the disease affected all age groups and both sexes. Slight female preponderance might be due to more susceptibility of females to immunological insult. Past and family history revealed onset of disease as acute febrile polyarthritis, affection of multiple family members during acute phase consistent with biting habits of Aedes aegypti mosquito,8 and recovery in most within few weeks. Appearance of chronic polyarthritis might be due to development of immunological phenomena after CHIK infection. Chronic disease affected all components of musculoskeletal system including joints, synovium, tendons and bursae. Soft tissue pain present may be attributable to myofascitis. Fatiguability and prolonged morning stiffness denote inflammatory nature of arthritis. Disease affected small and large joints of hands and feet in rheumatoid arthritis (RA) like distribution including MCPs, PIPs, wrists, elbows, shoulder, knee, ankles and MTPs. However in contrast to RA, DIP joints were also affected. None had affection of TM or sternoclavicular joint. Affection of spine and SI joints was not noted in the patients studied. All the patients had symptoms of moderate to severe degree to start with. Edema of hands and feet, a notable finding, may be inflammatory in nature and resembled RS3PE syndrome. One female patient developed flexion deformity of fingers one year later.

Mild anemia could be due to disease itself or nutritional. TLC, DLC and platelet counts were normal. Thrombocytosis

**Table 1 : Disease activity parameters assessment at follow up visits**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Parameter</th>
<th>Initial</th>
<th>3 months</th>
<th>6 months</th>
<th>1yr</th>
<th>2yrs</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>TJC</td>
<td>15.18 ± 3.9</td>
<td>11.93±3.27</td>
<td>9.7±4.06</td>
<td>8.31±2.8</td>
<td>7.2±2.8</td>
</tr>
<tr>
<td>2</td>
<td>SJC</td>
<td>10.00 ± 7.57±2.45</td>
<td>6.43±3.24</td>
<td>3.68±2.21</td>
<td>1.56±2.36</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>ESR</td>
<td>47.31 ± 33.81±7.95</td>
<td>24±6.95</td>
<td>25.75±7.15</td>
<td>22.31±6.85</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>HAQ</td>
<td>8.25 (46.5)</td>
<td>38 (10.5)</td>
<td>6 (6)</td>
<td>3.5 (3.5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>5</td>
<td>DAS</td>
<td>2.18 ± 0.63</td>
<td>1.92±(.58)</td>
<td>1.72±.48</td>
<td>1.35±.43</td>
<td>.96±.39</td>
</tr>
</tbody>
</table>

**Discussion**

Chikungunya virus causes acute febrile polyarthritis. Disease
Table 2: Statistical analyses of DAS score

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Group</th>
<th>Initial</th>
<th>2 yrs</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Mean</td>
<td>6.3856</td>
<td>4.1313</td>
</tr>
<tr>
<td>2</td>
<td>SD</td>
<td>0.8451</td>
<td>0.6600</td>
</tr>
<tr>
<td>3</td>
<td>SEM</td>
<td>0.2113</td>
<td>0.1650</td>
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<tr>
<td>4</td>
<td>N</td>
<td>16</td>
<td>16</td>
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Pair t(15) = 9.0005 (p < 0.0001), d.f. = 15, 95% CI = 1.2705 to 2.7882

SD- standard deviation, SEM- standard error of mean, N- no. of patients

(2 patients) indicate active disease. Marker of inflammation, ESR was raised in all. CRP (acute phase reactant) was raised in majority of patients and was normal in a few because of its property to rise and fall rapidly. Incidence of RF positivity (12.5%), was higher than that in the healthy adult population but lower than in patients of RA. RF could be false positive or its production could have been triggered by CHIK infection. Anti CCP antibodies were positive in 56.25% (with very high titers rarely), a figure much above that seen in general population (9), indicating their production in chronic phase of the disease in response to CHIK infection.

In our study, erosive disease developed in 1/1 patient who had both antibodies positive, 2/6 patients who had both antibodies negative and 2/9 patients who had one of the antibodies in serum. It would be worthwhile to see if these antibodies have any prognostic implication in PCCA.

Viruses are known etiological factors for development of RA. Considering appearance of anti CCP antibodies having high specificity for RA, it would be interesting to see if CHIK infection is triggering RA in genetically susceptible population or PCCA itself is a different entity which is seronegative, Anti CCP positive that has entirely different prognosis. Prolonged follow up, pathophysiologic and immunogenic studies will help to resolve the issue.

In our study, PCCA resembled RA clinically but had few unusual features. The differentiating features that we noticed were 1) onset as febrile polyarthritis in acute phase 2) H/O affection of multiple family members 3) DIP joint involvement 4) typical soft tissue pain 5) Presence of edema of hands and feet 6) Seronegativity in majority. It should be considered the close differential diagnosis of RA especially in CHIK affected areas.

Erosions were noted on X-rays and MRI as early as 8 months from the onset of infection confirming the erosive nature of the disease. Considering higher sensitivity of MRI over X Ray for detection of erosions, it could have picked up erosions early in those without erosions on X-Rays. Cost however was a major constraint. Synovial biopsy revealed development of nongranulomatous chronic synovitis following CHIK infection. It was negative for RT-PCR for viral RNA. Deformity occurred in one patient in spite of treatment.

We started the patient on NSAIDS (etoricoxib or Aceclofenac). Both worked well for symptom relief. Low dose steroids used initially were useful for early control of synovitis. Edema of hands and feet responded dramatically to steroids. Considering the immune mediated(10,11) nature of the disease, we started the patients on HCQ and SSZ combination. Most however required addition of MTX to the regimen, following which majority showed good improvement which was statistically significant (t(15) = 9.0005, p < 0.0001) stating its effectiveness in PCCA.

In a short term Indian study done earlier,6 combination of HCQ and MTX was found to be effective in chronic chikungunya arthritis. Another open pilot study4 also reveals effectiveness of chloroquine phosphate in chronic chikungunya arthritis with improvement in terms of morning stiffness and Ritchie articular index. Since combination therapy was use, doses of individual drugs required for disease control were small and hence better tolerated.

Thus early results of DMARDS like SSZ and MTX in PCCA are encouraging. More controlled studies are needed to note their effectivity, especially in achieving complete remission of the disease; the final goal of the treatment. PCCA simulates RA clinically and RF is absent in majority. Predominant antibody appears to be Anti CCP antibody. It is an erosive disease and produces nongranulomatous chronic synovitis. Limitations of our study were small sample size. Many more patients with history of febrile polyarthritis and affection of multiple family members fulfilled clinical criteria for PCCA. They could not be included in the study as they were CHIK IgM –ve. CHIK IgM negativity in them could be due to similar looking illness produced by another virus or disappearance of these antibodies from body at the time of evaluation. In absence of placebo control, bias in reporting could occur.

Conclusion

We conclude that chronic inflammatory polyarthritis does occur following chikungunya infection in 5.9% cases. It involves both large and small joints of hands and feet including DIP joints, is erosive and deforming. It is seronegative and anti CCP positive in most. It simulates RA clinically with few unusual features. DMARDS like SSZ and MTX are needed and are effective in treatment of PCCA.

References