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AUTOIMMUNE NEUROLOGICAL COMPLICATIONS OF CHIKUNGUNYA VIRUS – DOES IT REALLY TRIGGER

KEY WORDS: Chickungunya, Autoimmune neurological complications, immunotherapy.

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ABSTRACT

Introduction: Our aim was to study Chikungunya related autoimmune neurological complications (ANC) during the recent epidemic.

Material and Methods: This was a cross-sectional observational study of 164 Laboratory confirmed cases out of 1840 cases, which were screened for chikungunya virus infection from October 2017 to October 2018 and followed-up for 3 months. Laboratory, clinicoradiological data, predictors of neuraxial involvement, correlations, and outcome by immunomodulation were also analyzed.

Results: Out of the 164 confirmed Chikungunya cases, 48.13% developed overall neurological complications and only 23.8% cases had ANC. In ANC, majority had onset in the subacute (7-30 days) latency period without any mortality. We found Miller Fisher Syndrome (MFS) and peripheral ganglionic cyst formation as a new finding in ANC spectrum. Chikungunya patients were more prone to develop brachial plexus neuritis, polyneuritis cranialis and Guillain-Barre Syndrome (GBS). Significant (P<0.001) predictors of central nervous system involvement were anemia and elevated uric acid levels, whereas patients with higher mean body temperature and ANA positive status were more prone for peripheral nervous system involvement. Platelets counts and hemoglobin levels had a negative correlation whereas mean body temperature and alanine aminotransferase levels had a moderately significant positive correlation for development of ANC. Immunomodulatory therapy (IMT), if initiated after fever abatement, leads to significant clinical favorable outcome at 3 months, especially in patients with GBS, polyneuritis cranialis, and brachial plexus neuritis.

Conclusion: The spectrum of ANC in chikungunya infection may include MFS and peripheral ganglionic cyst formation. Early initiation of IMT, in the presence of significant predictors, may reduce ANC related morbidity.

Introduction:-

Chikungunya is a relatively rare and one of the most recent re-emerging infectious disease not only in India, but also worldwide. It is a benign form of viral infection caused by a RNA-virus belonging to genus Alphavirus[3,4] of Togaviridae family and is transmitted from primates to humans by Aedes aegypti mosquito. The first outbreak of Chikungunya virus infection (CHIKV) occurred in East Africa (Tanzania and Uganda) in 1952 and 1953. The name is derived from the makonde word that means " that which bends up" in reference to the stooped posture developed s a result of the arthritic symptoms of the disease. In 1999, an outbreak occurred in Port Klang in Malaysia. Subsequent epidemics have been reported from austral Africa (Zimbabwe and South Africa), West Africa (Senegal and Nigeria), central Africa (Central African Republic, and democratic republic of the Congo[5]). Southeast Asia (Philippines, Malaysia[2], Cambodia), and the Indian subcontinent (Pakistan and southern India). The first documented Asian outbreak was in 1958. In India, the first outbreak was reported in 1963 in Calcutta[7]. Subsequent epidemics have been reported from other parts of India, Kolkata, Vellore, Barsi and Nagpur[8,10].Many outbreaks of chikunguniya have occurred simultaneously during dengue outbreaks[9]. In December 2005, affecting a large population in southern and central India (Tamil Nadu, Karnataka, Kerala, Andhra Pradesh, Maharashtra) over 2000 cases of CHIKV fever were reported from Malegaon town in Nasik district of Maharashtra between February and March 2006. In may 2006, a large outbreak occurred in Nagpur district of Maharashtra[6].

Neurological complications of CHIKV infection being reported from last decade but experience of autoimmunity were lacking and have been reported only recently[15]. In the present study our experience of neurological complications in CHIKV infection and mainly emphasized on triggering to autoimmunity for nervous system in the recent epidemic in Kota district of Rajasthan is reported.

In our study we categorized neurological manifestations associated with chikungunya virus into (1) acute complications (AC) leading to encephalitis and myositis, (2) vascular neurological complications or vasculitis effects leading to cerebrovascular accident, cerebral venous sinus thrombosis (3) metabolic neurological complications resulting in encephalopathy, hyponatremic encephalopathy and hypokalemic paralysis, and (4) autoimmune neurological complications which include guillain-barre syndrome, brachial and lumbosacral plexitis, cranial neuropathies and mylopathy. There is paucity of literature on chikungunya related ANCS. In this study, we focused on the variability in clinical presentations, investigations and role of immunomodulation in ANC associated with Chikungunya Virus (CHIKV).

Material and method:-

This study was cross sectional observational study of 79 ANC cases from 164 laboratory confirmed CHIKV cases from October 2017 to October 2018 at the government medical college and attached groups of hospitals, Kota, Rajasthan with a follow-up for 3 months. All of the patients had typical clinical features of CHIKV infection fever, headache, body ache, myalgia, and joint pains with or without swelling and without hemorrhagic rash. We analyzed laboratory and clinic-radiological data, predictors for development of ANC. Outcome was measured for short term

immunomodulatory therapy (IMT). Informed consent was taken from all included patients.

CHIKV was diagnosed on the basis of positive serum immunoglobulin M antibody. The serum IgM antibody was analyzed by enzyme linked immunosorbent assay (ELISA) method using an IgM antibody capture ELISA (MAC-ELISA, National institute virology, Pune, India). It was a qualitative analysis, and hence the titers were not measured.

The baseline characteristics and epidemiological data including age and sex of all the included patients were recorded. The routine laboratory investigations including hemoglobin level, total leucocyte count, platelet count, hematocrit. Erythrocytic sedimentation rate (ESR), rheumatoid factor, random blood sugar, liver function test, renal function test creatine kinase, prothrombin time, serum electrolytes, anti nuclear antibody ANA, uric acid levels and ELISA for human immunodeficiency virus were performed in all the patients.

Nerve conduction studies, electromyography, electroencephalography, visual evoked potential, and neuroimaging studies including magnetic resonance imaging of the brain and spine were performed in patients, as indicated by clinical presentation. The cerebrospinal fluid analysis including IgM antibody for Chikungunya virus was performed in indicated patients. Serum and CSF samples were also tested for herpes simplex virus (HSV), Mycobacterium tuberculosis, cytomegalovirus and varicella zoster virus in patients with myelopathy, polyneuritis cranialis, and plexitis. Tests for antinuclear antibody, antidouble standard, anticyclic citrullinated peptide antibody, antiphospholipid antibodies, antiaquaporin-4 antibody and anti-ganglioside antibody panel were also carried out in indicated cases to access possibility of autoimmune diseases.

Latency period for the onset of ANC was calculated from the abatement of fever. According to it, patients were classified as acute (7 days), subacute (7-30 days), and chronic (>30 days). On the basis of IMT received, patients were divided into two categories, i.e. those who received single IMT and those who received double IMT.

The outcome was defined at the end of 3 months follow up on the basis of modified rankin scale. Complete recovery and favorable outcome was labeled when mRS≤2, whereas partial recovery when mRS≥3.

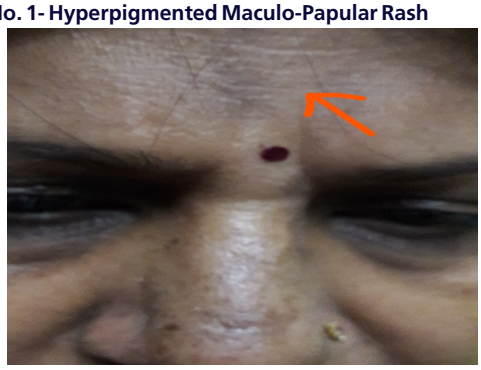
The mean, range, and standard deviation were calculated wherever applicable. Fisher's exact test was used to calculate whether there was a significant association between categorical variables. The P-value was derived from the F-statistic score by making use of the F cumulative distribution function. Chi-square test was used for testing categorical data and dense contingency table. Significance level was considered as P value <0.05. A possible correlation was assessed using pearson correlation coefficient. The pearson correlation coefficient was used to measure the strength of a linear association between two variables, where the value r=1 means a perfect positive correlation and the value r=-1 means a perfect negative correlation. For statistical analysis of all the above data we used the statistical package for the social sciences version 17.0 software.

Result:-

A total of 164 patients were diagnosed to be Chikungunya positive during the study period. Most common presentation was fever with joint pain which was seen in 46.95% followed by patients with fever with rash (45.12%) and fever with pigmentation (7.92%).

The typical rash that was observed in these patients developed on 4-5th day but hyperpigmented or darkly pigmented mild itching maculopapular rash which was predominantly seen on Nasal bridge, central part of forehead and dorsal aspect of extremities developed after a week simulating benign lichenoid keratosis (BLK) or lichen planus like keratosis. This rash of BLK was self limiting completely after two to three month of illness.

Fig. No. 1- Hyperpigmented Maculo-Papular Rash



Out of all 164 patients, neurological involvement was seen in 78 patients. Female:male ratio was 1.106. Age range was 3-67 years.

Neurological complications associated with Chikungunya virus in our study included acute complications, Vascular complications (Stroke, Cerebral venous sinus thrombosis, SAH), metabolic complications and autoimmune neurological complications (Table 1).

Table 1: Demographic and clinical profile of the Chikungunya virus infected patients

Characteristics	Numbers	Percentage
Total confirmed cases	164	
Fever with rash Fever with rheumatism Fever with pigmentation (including BLK)	74 77 13	45.12 46.95 7.92
Total Neurological affected cases	78	
Male Female	35 43	21.34 26.21
Age range in years	3-67	
Central nervous system involvement Peripheral nervous system involvement	30 48	18.29 29.26
Acute Neurological complications Encephalitis Myositis	18 02 16	10.97
Vascular neurological complications Stroke Cerebral venous thrombosis SAH	06 04 01 01	03.65
Metabolic neurological complications CHICKV encephalopathy Hyponatremic encephalopathy Hypokalemic paralysis	15 09 05 01	09.75
Autoimmune neurological complications AMSAN AMAN AIDP MFS- variant Brachial plexus neuritis Lumbosacral plexities Peripheral gaglionic cyst formation Polyneuritis cranialis Myelopathy Optic neuritis Carpal tunnel sytndrome (CTS)	39 08 03 02 01 07 01 02 02 03 01 09	23.78
Mortality	01	0.61

BLK: Benign Lichenoid Keratosis, AIDP: Acute Inflammatory Demyelinating Polyneuropathy, AMAN: Acute Motor Axonal Neuropathy, AMSAN: Acute Motor Sensory Axonal Neuropathy, MFS : Miller Fischer Syndrome, SAH: Subarachnoid haemorrhage.

The mean age of the patients was 31.09 years (range 3-67 years). Out of 78 neurological affected patients, 30 had central nervous system and 48 had peripheral nervous system involvement. Out of 78 diagnosed patients, 39 patients developed ANC. Majority of the cases developed ANC in the subacute latency period (Table2).

Table 2: Characteristics of Chikungunya related Neurological Complications:

	Total (78)	PNS (48) Involvement	CNS (30) Involvement
Age range in years	3-67	7-67	3-59
Latency period from abatement of fever			
Acute (<7 days)	22	15	08
Subacute (>7-30 days)	45	26	18
Chronic (>30 days)	12	07	05

CNS: Central Nervous System, PNS: Peripheral nervous system

Comparison of the presumed risk factors in patients with CNS versus those with PNS involvement revealed that significant predictors of CNS involvement were anemia (P=0.002) and hyperuricemia, whereas higher mean body temperature (P=0.0010) and ANA positivity were more associated with PNS involvement. Other parameters, diabetes, hypothyroidism, and obesity were not found to differ significantly between the two groups (Table 3).

Table 3: Presumed risk factors for autoimmune neurological complications (ANC) by chikungunya virus infection

Risk Factor	Total (78)	PNS(96)	CNS(92)	P Value
Anemia	86	34	52	0.024 (Significant)
Low platelets	76	42	34	0.65
ANA	61	42	19	0.023(Significant)
Hyperuricemia	50	12	38	<0.001(Significant)
High MBT	102	76	26	<0.001(Significant)
Diabetes	08	02	06	0.34
Hypothyroidism	04	02	02	0.99
Pregnancy	10	0	04	0.99
Obesity	08	0	08	0.34

MBT: Mean Body Temperature, ANA: Anti Nuclear Antibody

Correlation analysis of the various predictors and development of ANC revealed that platelet counts and hemoglobin levels had a negative correlation whereas uric levels, mean body temperature and SGPT levels had a moderately significant positive correlation for the development of ANC. No correlation was observed between levels of SGOT with ANC(Table 4).

Table 4: Correlation of variables in autoimmune neurological complications by Chikungunya virus infections

Variables	Correlation coefficient (r-value)	P- Value
Age	0.13	0.264
Hemoglobin	-0.63	0.028
Uric acid levels	0.67	0.0001
Platelets count	-0.35	0.0017
Temperature	0.74	0.0001
SGPT	0.23	0.041
SGOT	0.11	0.314

SGOT: Serum Glutamic Oxaloacetic Transaminase, SGPT: Serum Glutamic Pyruvate Transaminase.

GBS was observed in 14 cases. Mean latency period for the development of GBS was 11.78 (7-30 days). Majority of the patients presented with fever with polyarthralgia with minimal weakness in 11 cases whereas severe presentation was found in 3 cases who required ventilatry support. Minimal weakness of 11 cases were included in GBS because of fulfilling criteria on clinical and electrophysiological evaluation. Early neuropathy was observed in 9 cases. These presented within week of the onset of fever.These patients had additional encephalopathy or myelopathy in 3 cases.

Late neuropathy occurred in 7 cases and presented 2-3 weeks after the onset of fever .Most common pattern that was observed in electrophysiological studies was mixed pattern. Neurophysiological study revealed AMSAN subtype as the most common variety in 8 cases. Out of the 14 GBS patients,1 was diagnosed as MFS variant, which had ganglioside antibody.

Three patients had only myelopathy as a complication of Chikungynya infection. The latency period was 1 week and during course of illness ascending pattern was there but severity in lower limbs were more than upper limbs. Patients often first developed retention of urine and then showed paraparesis. The CSF showed raised proteins and lymphocytic pleocytosis in all.The MRI changes showed more than 3 segment involvement in one patient. Other investigations suggesting possibilities of inflammatory, infectious and autoimmune LETM were negative, which included Anti-NMO, OCB, ACE level, VZN, HIV, HSV, ANA, CMV and anti TPO. Functional outcome after 3 months follow up in 2 patients who received MPS was favorable (mRS<2) whereas it was poor (mRS>3) in 1 patient who was treated with IVIG.

The diagnosis of brachial plexus neuritis was also established in 7 patients. Five patients had right upper limb involvement. Mean latency period was high (18.35±2.01 days); minimum 7 days and a maximum of 29 days. On Neurophysiological evaluation, stimulation of the proximal nerves of the upper limbs (axillary, musculocutaneous, long thoracic, suprascapular radial, median, and ulnar) revealed axonal changes in 4 patients, demyelinating changes in the 2 patients and mixed in 1. One patient had clinical features of unilateral lumbosacral plexitis in the form of neuropathic pain, weakness, and atrophy of proximal musculature in the lower limbs following Chikungunya infection, NCS was suggestive of axonal pattern. Gadolinium-enhancing MRI dedicated to lumbosacral spine and plexus was within normal limits however, CSF showed albuminocytological dissociation. All patients achieved complete clinical recovery after a course of intravenous MPS.

One patient had isolated painful optic neuritis. Involvement was unilateral with delayed P-100 latency in VEP and no disc leakage in retinal fluorescein angiography. A brain and orbital MRI study revealed mild enhancement of optic nerves. After 5 day course of MPS , complete clinical recovery was achieved after 10 days.

Two patients with isolated cranial nerve involvement, in the background of normal biochemical and radiological investigations and exclusion of all possible etiologies, were kept as a clinical diagnosis of polyneuritis cranialis. Involved cranial nerves were 7,9,10th in one and 6,7,3 in another patient. Unilateral involvement was observed in 1 patient whereas 1 patient had bilateral involvement. 1 patient received IVIg whereas 1 received MPS. Complete response was observed in the both.

Fig.No. 2- Polyneuritis Cranialis

On immunomodulatory therapy analysis of 14 patients of GBS, 10 patients received MPS whereas Immunoglobulin and Plasmapheresis was administered in 2 and 1 patient respectively. Whereas remaining 1 patient, who was diagnosed as MFS, received two IMTs (IVIg and Steroids). Out of 14 GBS patients, 10 patients were treated with MPS in presence of rheumatism and mild severity. The number of patients showing complete response on follow up were 2 (IVIg), 1 (plasmapheresis), and 6 patients (Steroids). MFS patient who received both IVIg and steroids, showed complete response on follow up. The percentage of patients who received IMT, showing complete response were as follows: 100 % in the IVIg ,plasmapheresis and double IMT group whereas 60 % in patients receiving only steroids. (Table 5)

Table 5: Response of Immunomodulatory therapy in GBS patients

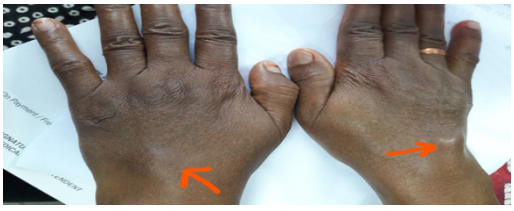
IMT	Number of Patients N=14	Complete response (% response)
Immunoglobulin	2	2(100%)
Plasmapheresis	1	1(100%)
MPS	10	6(60%)
Two IMT	1	1 (100%)

MPS: Methylprednisolone, IMT: Immunotherapy

Stroke was also observed in 4 patients after Chikungunya infection. Initial CT was grossly within normal limits. However MRI brain was suggestive of characteristic imaging findings. There were multiple hyperintense dots on diffusion weighted images that were considerably marked in comparison to that in T2 and flair. Rarely, the T1 view showed the dots to be hypodense.

The new complication observed in our study was peripheral nerve ganglion cyst in 2 patients of which at wrist in 1 and elbow in one after Chikungunya infection. Theses cysts were mildly tender and recovered after oral four weeks of steroid treatment.

Fig. No. 3- Peripheral Nerve Ganglion Cyst



Carpal tunnel syndrome was also observed in 9 patients. This appeared in second month of Chikungunya infection, characteristically associated with wrist synovitis and morning stiffness at wrist joints and electrophysiologically associated with predominantly motor median axonal neuropathy along with ulnar neuropathy however isolated demyelinating median neuropathic pattern was also observed but only in 4 patients. Apparently, carpal tunnel syndrome connotation does not only due to it was secondary to synovitis but having some autoimmune site predilections of nerve at wrist joint along with other inflammatory joint process.

We also analysed ANA status in all patients with neurological involvement. ANA positivity was present in total 61 patients (37.19%). Females had a higher positive percentage (23.17%) compared to males (14.02%).Patients with autoimmune neurological complications had a higher positive percentage (20.12%) compared to other complications. (Table 6)

Table 6: ANA status in Chikungunya virus related various Neurological Complications

		ANA Positivity (%)from total no of cases
Total cases (including BLK)	164	83 (50.61%)
Total Neurological affected cases	78	61 (37.19%)
Male	35	23 (14.02%)
Female	43	38 (23.17%)
Age range in years	3-67	11 (6.70%)
Acute neurological	18	
Encephalitis	02	
Myositis	16	
Vascular neurological complications	06	4 (2.43%)
Stroke	04	
Cerebral venous thrombosis	01	
SAH	01	
Metabolic neurological complications	15	13 (7.92%)
CHICKV encephalopathy	09	
Hyponatremic encephalopathy	05	
Hypokalemic paralysis	01	
Autoimmune neurological complications	39	33 (20.12%)
AMSAN	08	
AMAN	03	
AIDP	02	
MFS-Variant	01	
Brachial plexus neuritis	07	
Lumbosacral plexities	01	
Peripheral gaglionic cyst formation	02	
Polyneuritis cranialis	02	
Myelopathy	03	
Optic neuritis	01	
Carpal tunnel syndrome	09	

BLK: Benign Lichenoid Keratosis, AIDP: Acute Inflammatory Demyelinating Polyneuropathy, AMAN: Acute Motor Axonal Neuropathy, AMSAN: Acute Motor Sensory Axonal Neuropathy, MFS : Miller Fischer Syndrome, SAH: Subarachnoid haemorrhage.

Discussion:-

This study is probably the first report of large series of autoimmune neurological complications following CHIKV infection from India. Neurological complications were seen in 47.56% of 164 patients with CHIKV infection registered in our institute during the recent epidemic.

The usual clinical picture of infection is fever, malaise, rash, headache, nausea, body ache and joint pains.[1] The fever lasts for 3-6 days only but arthropathy and body aches are severe and persisting. The illness is a self limiting one however, the arthropathy may last 3-6 months and occasionally longer, and this is an exception to the general rule that viral arthritis lasts for less than 8 weeks[3].

Various neurological complications in patients of chikungunya have been reported in India[12,13] as well as during the recent French reunion islands outbreak. It remains uncertain whether neurological symptoms are due to persistence of the virus or inappropriate immune response. The genetics of Chikungunya virus might play a key role in determining the course of neuropathogenesis[14]. The severity of the disease in the 2006 outbreak in particular the associated neurological complications may be related to the mutated CHIKV[11].

There is abundant literature on the spectrum of neurological manifestations associated with Chikungunya virus, however, there is insufficient data on autoimmune neurological complications because majority of the published articles have not emphasized it. The true incidence, prevalence, latency period, predictors of neurological involvement and management consensus related to autoimmune neurological complications associated with Chikungunya virus is not clearly mentioned in the literature. During our study, we also encountered different views concerning immunomodulation treatment, especially regarding optimal timing for initiation, duration of therapy, and whether there will be clinical benefit or not. By this study we have been able to answer these questions to some extent.

Patients in our study belonged to all age groups ranging 3-67 years (mean age 27 years). Female preponderance in the incidence of ANC was observed in our study.

Stroke was also observed in 4 patients after Chikungunya infection. Initial CT was grossly within normal limits. However MRI brain was suggestive of characteristic imaging findings. There were multiple hyperintense dots on diffusion weighted images that were considerably marked in comparison to that in T2 and flair. Rarely, the T1 view showed the dots to be hypodense. Multiple white dots have been described before in other encephalitides, e.g. Nipah virus encephalopathy, Rocky mountain spotted fever and Lyme disease. In the last two cases, vasculitis in the brain is demonstrated. Similar dots may also be rarely observed in cryptococcal meningitis and have been described in cerebral malaria, although we have never observed these. They pointed out that the lesions were clearly observed in T2 and they were considerably fewer in Diffusion and they enhance on diffusion. This was not observed in our cases, where lesions were observed to

be clearer on Diffusion than in T2.

In our study, autoimmune neurological complications were based on biological confirmation; neurophysiological in GBS, MFS, brachial and lumbar plexitis, peripheral nerve ganglion cyst and carpal tunnel syndrome and by neuro imaging and /or clinical in myelopathy, polyneuritis cranialis and optic neuritis.

ANC such as GBS and CTS can be explained on the basis of autoimmunity, molecular mimicry, or non specific activation of auto-reactive T cell clones, leading to the destruction of the myelin sheath antigens[12]

The associations of myelopathy with Chikungunya virus is exceptional and suggest an acute infectious myelopathy or immune-mediated process where the virus acts as a "trigger" for the inflammatory process targeting the myelin sheath cells.

In CHIKV, spinal cord tropism was observed in our study in 3 patients, of which one raised a suspicion of NMO spectrum-like disorder because had more than 3 segment involvement. It started a few days after fever. Patients first developed retention of urine and then showed paraparesis. Usually, the upper limbs were more or less not involved. The CSF showed raised proteins and lymphocytic pleocytosis in all. Functional outcome after 3 months follow up in 2 patients who received MPS was favorable (mRS≤2) however it was poor (mRS≥3) in one patient who received IVIG. With our study, we would like to suggest that CHIVK associated myelopathy may be included as a part of NMOSD evaluation. A strong argument for the hypothesis of immune mediated myelitis is the delay between the end of the fever and the onset of neurological symptoms and the fact that no patient complained of any neurological manifestations during the acute phase of Chikungunya infection. Further, the reversibility of signs and symptoms with IV corticosteroid administration is better in case of immune mediated myelitis, which is not the case in infectious myelitis. As for the diagnosis, post infectious myelitis, unlike infectious myelitis, may be associated with a higher frequency of normal CSF. In our study, CSF examination did not show any significant changes in cellularity or chemistry, further reinforcing the hypothesis of an immune mediated mechanism.

GBS was observed in 14 patients, majority of which were AMSAN variant. Out of all the GBS patients, 1 case was diagnosed as probable MFS. We also endorse that Chikungunya infection should be routinely looked for in GBS cases in an endemic zone. The percentage of patients, who received only single IMT, showing complete response were as follows: 100% in plasmapheresis and IVIg group, and 60 % in patients receiving only steroids. Although IVIg and plasmapheresis are considered as the first line treatment modality for GBS patients, however the patients receiving only steroids also showed good clinical improvement. One hypothesis for this response may be that post chikungunya illness including GBS show a good clinical response to steroids, which was observed in other chikungunya related ANC of this study. However this hypothesis needs validation by further studies.

Brachial plexus neuritis is a neurological disorder characterized by severe neuropathic pain, weakness, and mild weakness of the proximal musculature, mainly of the upper limbs because of involvement of the brachial plexus. The diagnosis of brachial neuritis was also established in 7 patients in our study. Mean latency period was higher. One patient had clinical features of unilateral lumbosacral plexitis following chikungunya infection. All patients achieved complete clinical recovery after a course of intravenous MPS. We hypothesize that post chikungunya infection leads to autoimmune response against myelin sheath or other self antigens causing brachial and lumbosacral neuritis due to patchy demyelinaiton of plexus. Which is similar to other established virus induced immune mechanism.

Cranial nerve involvement in CHIKV was also observed in our study. Bilateral or unilateral cranial nerve involvement associated with CHIKV may be observed. Complete response was achieved by intravenous MPS followed by 3 weeks oral steroid course.

One patients of optic neuritis was related to immune mediated involvement of optic nerve because ANA positivity, latency period and complete clinical recovery with steroids suggested an immune mediated involvement. Optic nerve involvement has been described from south India. Mittal et al described 14 cases with recent chikungunya infection who had optic nerve involvement. In these cases, 19 eyes were affected, 8 showed papilitis, 4 showed retrobulbar neuritis, 4 showed retrochiasmal optic neuritis and 3 showed neuroretinitis with incomplete macular star. In five cases, the visual problem appeared with the initial illness and in the rest after a mean of 11.0 days after they were symptom free from the initial fever. CT and MRI were normal in all the cases. 10 patients improved with methylprednisolone.

Significant (P<0.001) predictors of CNS involvement are anemia and elevated uric acid levels whereas patients with higher mean body temperature and ANA positivity are more prone for PNS involvement. Platelets counts and hemoglobin levels have a negative correlation whereas mean body temperature and alanine aminotransferase levels have a moderately significant positive correlation for the development of ANC.

We also analyzed ANA status in all patients with neurological involvement. ANA positivity was present in total 61 patients (37.19%). Females had a higher positive percentage (23.17%) compared to males (14.02%). Patients with autoimmune neurological complications had a higher positive percentage (20.12%) compared to other complications. The peculiar finding on qualitative analysis was that of speckled pattern.

There were 1 death among all patients with neurological involvement who was 55 years old, had severe encephalopathy at onset and additional septicemia. Only CT could be performed and patient was treated with intensive care.Post mortem was not done.

Limitations of the study:
(1) It is an observational study.
(2) Majority of the patients were treated with intravenous methylprednisolone as the IMT.
(3) The role of immunomodulatory therapy needs to be further confirmed by large scale randomized control studies
(4) Many treating physicians were hesitant to give IMT as it has not been studied and no consensus exists on its administration.

Conclusions:

The study results may help to extend Chikungunya related ANC spectrum by new observations such as the spectrum of ANC is vast and may include MFS, peripheral ganglionic cyst formation and BLK. Patients with presumed risk factors and predictors such as high hematocrit value, liver dysfunction and high mean body temperature, ANA positive status have a statistically significant tendency to develop ANC following Chikungunya virus infection. Positivity of ANA and protean neurological immune mediated manifestations and BLK definitely cast doubt for triggering autoimmunity by CHIKV. Early initiation of IMT, in the presence of significant predictors, may reduce ANC related morbidity. For further validation of it ,more studies are to be needed.

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