Original Article

Neurological complications of Chikungunya virus infection

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Abstract

Background: In May 2006, there was a large Chikungunya virus infection (CHIKV) outbreak in the Nagpur district of Maharashtra, a province in western India. Usually, CHIKV is a self-limiting febrile illness. However, neurological complications have been described infrequently. **Aim:** To study the clinical characteristics of various neurological complications associated with CHIKV infections. **Materials and Methods:** Patients with neurological complications following CHIKV infection during the outbreak were the subjects of the study. On the basis of clinical features and investigative findings, patients were grouped into various neurological syndromes: Encephalitis, myelopathy, peripheral neuropathy, myeloneuropathy, and myopathy. Cerebrospinal fluid (CSF) samples were also collected for biochemical and serological studies. **Results:** Of the 300 patients with CHIKV infection seen during the study period, June–December 2006, 49 (16.3%) [M : F: 42:7] had neurological complications. The neurological complications included: Encephalitis (27, 55%), myelopathy (7, 14%), peripheral neuropathy (7, 14%), myeloneuropathy (7, 14%), and myopathy (1, 2%). Reverse Transcriptase polymerase chain reaction (RT-PCR) and real-time PCR was positive in the CSF in 16% and 18%, respectively. **Conclusion:** Recent CHIKV infection was associated with various neurological complications, suggesting neurotropic nature of the virus. The outcome of the neurological complications is likely to be good.

Key words: *Chikungunya, neurological complications, encephalitis, myelitis, peripheral neuropathy, cerebrospinal fluid*

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Introduction

Chikungunya is a relatively rare and benign form of viral infection caused by a RNA-virus belonging to genus *Alphavirus* 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.[1] In 1999, an outbreak occured in Port Klang in Malaysia.[2] 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),[3-5] Southeast Asia (Philippines, Malaysia, 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[6] Subsequent epidemics have been reported from other parts of India, Kolkata, Vellore, Barsi, and Nagpur.[7-10] The recent epidemic started in December 2005,[6] affecting a large population in southern and central India (Tamil Nadu, Karnataka, Kerala, Andhra Pradesh, Maharashtra). Over 2,000 cases of CHIKV fever were reported from Malegaon town in Nasik district of Maharashtra between February and March 2006.[11] In May 2006, a large outbreak occurred in Nagpur district of Maharashtra.

Neurological complications of CHIKV infection are infrequent and have been reported only recently.[12] In the present study our experience of neurological complications in CHIKV infection in the recent

epidemic in Nagpur district of Maharastra is reported.

Materials and Methods

Three hundred patients of clinically suspected CHIKV infections were enrolled for the study from July–December 2006 and followed up for any neurological complications until April 2007 at the Central India Institute of Medical Sciences (CIIMS), Nagpur, India. 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. The study had the approval of Institutional Ethics Committee, CIIMS, Nagpur.

Forty-nine patients who developed neurological symptoms within two months of CHIKV infections were hospitalized. All had detailed neurological evaluation and blood investigations, Depending on the neurological syndrome, patients were further investigated: CSF analysis, electrodiagnostic tests, electroencephalography (EEG), evoked potential studies, and neuroimaging, computerized tomograpy (CT) and/or magnetic resonance imaging (MRI). Molecular tests Reverse Transcriptase polymerase chain reaction, [RT-PCR], real-time PCR) and virus isolation were done in patients for whom CSF study was done.

On the basis of clinical features and investigation findings patients were grouped into various neurological syndromes: Encephalitis, myelopathy, peripheral neuropathy, myeloneuropathy, and myopathy. Patients with entrapment neuropathy were not included in the study. Patients were given supportive care as per the clinical syndrome and the course of the illness. Some received a course of methylprednisolone 1 g daily for 3–5 days.

Results

Of the 300 patients with CHIKV infection seen during this epidemic, 49 (16.3%) patients developed neurological complications There were 42 males and 7 females and the age was above 20 years in all except one. The neurological syndromes observed include: Encephalitis (27, 55.1%), myelopathy (7, 14.3%), neuropathy (7, 14.3%), myeloneuropathy (7, 14.3%), and myopathy (1, 2%) [Table 1]. Majority of the patients developed neurological complications within 20 days of onset of CHIKV infection. RT-PCR and real-time PCR was positive in eight (16%) and nine (18%) cases, respectively. However, positivity for virus isolation was only noted in one case. Of the 27 patients with encephalitis, 16(59%) presented with abnormal behavior and 6 (22%) each with impaired level of consciousness and extrapyramidal features [Table 2]. EEG was done on all patients of the encephalitic group. It did not reveal any specific information except generalized intermittent slow wave dysrhythmia. Of the 14 patients with myelopathy and myeloneuropathy, only in 3 signal alterations on MRI suggestive of demyelination were seen in the cord [Table 3]. In the 14 patients who had electrodiagnostic studies, all had demyelinating neuropathy. CT brain was done in 20 patients with encephalitis and was essentially normal in all the patients. Of the 4 patients who had MRI brain, one had white matter signal changes.

CSF analysis was done in 38 patients [Table 4], Of the 20 patients with encephalitis, proteins were raised in 14, sugar was low in 3, and cells were increased in 6. Of the six patients with myelopathy, proteins were raised in two. Of the six patients with neuropathy group, five had raised proteins. Of the six patients with myeloneuropathy, five had raised proteins and two had reduced sugar.

The outcomes were good. Of the 49 patients, there were three deaths, two with encephalitis and one with myeloneuropathy and 37 (75.5%) patients had good outcome [Table 1]. Of the patients 49 patients, 34 (69.4%) were given corticosteroid treatment and the remaining 15 patients were given supportive treatment. Of the 34 patients given corticosteroids, 25 (73.5%) improved whereas of the patients receiving only supportive treatment, 12 (80%) patients improved.

Table 1: Latency between disease and onset of neurological symptom, RT-PCR, and real-time PCR, virus isolation, and outcome in patients with various neurological syndromes

Neurological syndromes		Mean ± 2SD	Latency between disease and onset of neurological symptoms (days)					RT-PCR (%)	Real-time PCR (%)	Virus isolation	Outcome		
			<5	>5–10	>10–20	>20–30	>30				Improved	Static	Expired
Encephalitis	*n* = 27	62.11 + 14.15	12	7	5	0	3	4 (15)	4 (15)	-	21	4	2
Myelopathy	*n* = 07	64.57 + 18.67	4	1	1	1	0	1 (14)	2 (28)	1	5	2	-
Myelo-neuropathy	*n* = 07	59.28 + 7.99	3	2	2	0	0	1 (14)	1 (14)	-	4	2	1
Peripheral neuropathy	*n* = 07	35.28 + 11.69	1	3	3	0	0	1 (14)	1 (14)	-	6	1	-
Myopathy	*n* = 01	-	-	-	-	1	-	1 (100)	1 (14)	-	1	-	-
Total	*n* = 49	-	20	13	11	2	3	*n* = 8 (16)	*n* = 9 (18)	*n* = 1	*n* = 37	*n* = 9	*n* = 3

Discussion

This study is probably the first report of large series of neurological complications following CHIKV infection from India.Neurological complications were seen in 16.3% of 300 patients with CHIKV infection registered in our institute during the 2006 epidemic. This high frequency of neurological complications may be related to referral bias. Our institute is the primary referral center for neurological diseases from Vidarbha, part of Maharastra and adjoining parts of Madhya Pradesh Chhatisgarh, and Andhra Pradesh.

Most often, CHIKV infection is a self-limiting illness. Neurological complications are infrequent and have been reported during the first Indian outbreak as well as during the recent French Reunion islands outbreak.[13] It remains uncertain whether neurological symptoms are due to persistence of the virus or inappropriate immune response.[14,15] The severity of the disease in the 2006 outbreak, in particular the associated neurological complications may be related to the mutated CHIK.[16] In our series 46.5% of patients with neurological complications were above 60 years of age. The time interval between CHIKV infection and neurological complication was quite variable. 47% presented within one week and 6% after one month. Of the neurological complications, encephalitis was the common presenting syndrome in 55% of patients. In our series the neuropathy was predominantly demyelinating type. Only in 3 of the 14 patients with myelopathy/myeloneuropathy, MRI showed signal changes in the spinal cord suggestive of demyelinating pathology. Similar signal changes were also seen the study by Wadia.[12] Most of the patients (75, 5%) showed good neurological recovery at 3 months of follow-up and 9 patients had no much improvement in the neurological deficits. There was no difference in the outcomes between patients treated conservatively and patients treated with steroids. There were 3 (6%) deaths and all the deaths were attributable to the medical complications. Our study suggests that the outcome of the neurological complications following CHIKV infections are likely to be good and the mortality is more related to the systemic complications.

Table 2: Clinical manifestations in the encephalitic group (*n* = 27)

Clinical manifestations	No. of patients	%
Impaired level of consciousness	6	22.22
Abnormal behavior	16	59.25
Convulsions	3	11.11
Cranial nerve involvement	1	3.70
Extrapyramidal features	6	22.22
Meningeal irritations	2	7.40
Features of neuropathy	2	7.40
Features of myeloneuropathy	4	14.81

Table 3: Clinical manifestations and investigation results in myelopathy, myeloneuropathy, and peripheral neuropathy group

Clinical manifestations and investigations	No. of patients		
	Myelopathy *n* = 7	Myeloneuropathy *n* = 7	Peripheral neuropathy *n* = 7
Paraparesis	6		-
Quadriparesis	1	6	7
Urinary retention	6	1	-
MRI spine	7	5	ND
Normal	6	3	-
Abnormal	1	3 (*n* = 5)	-
EMG NCV	ND	-	-
AIDP	-	7	7
AMAN	-	-	-
MSAN	-	-	-

ND - Not done, AIDP - Acute inflammatory demyelinating polyradioneuropathy, AMAN - Acute motor axonal neuropathy, AMSAN - Acute motor sensory axonal neuropathy

Table 4: Biochemical and microscopic findings in CSF of patients with neurological complications (*n* = 38)

CSF parameters	Neuromanifestations group			
	Encephalitis *n* = 20	Myelopathy *n* = 6	Neuropathy *n* = 6	Myeloneuropathy *n* = 6
Proteins (mg%)				
<45	6	4	1	1
>45–60	3	1	0	2
>60–100	9	0	0	1
>100	2	1	5	2
CSF sugar/ blood sugar ratio				
>5–0	17	6	6	6
>03–0.5	3	-	0	2
<0–3	0	-	0	0
CSF cellularity/cc				
<5	14	4	6	6
<5–50	4	2	0	0
>50	2	0	0	0

References

1. Sudeep AB, Parashar D. Chikungunya: An overview. J Biosci 2008;33:443-9.
2. Lam SK, Chua KB, Hooi PS, Rahimah MA, Kumari S, Tharmaratnam M, Chuah SK, Smith DW, and Sampson IA. Chikungunya infection - an emerging disease in Malaysia. Southeast Asian J Trop Med Public Health 2001;32:447-51.
3. Jupp PG, McIntosh BM. Chikungunya virus disease. In: Monath TP, editor. The arboviruses. Epidemiology and ecology. Boca Raton, FL: CRC Press; 1988. p. 137-57.
4. Monath TP, Heinz FX. The alpha viruses. In: Fields BN, Knipe DM, Howley PM, editors. Fields virology. 3rd ed. Vol 1. Philadelphia, PA: Lippincott-Raven; 1996. p. 843-98.
5. Pastorino B, Muyembe-Tamfum JJ, Bessaud M, Tock F, Tolou H, Durand JP, Peyrefitte CN. Epidemic resurgence of Chikungunya virus in Democratic Republic of the Congo: Identification of a new central African strain. J Med Virol 2004;74:277-82.
6. Arankalle VA, Shrivastava S, Cherian S, Gunjikar RS, Walimbe AM, Jadhav SM, *et al.* Genetic divergence of Chikungunya viruses in India (19633-2006) with special reference to the 2005-2006 explosive epidemic. J Gen Virol 2007;88:1967-76.
7. Pavri KM, Banerjee K, Anderson CR, Aikat BK.Virological and serological studies of cases of haemorrhagic fever in Calcutta: Material collected by the Institute of Post-Graduate Medical Education and Research (IPGMER), Calcutta. Indian J Med Res 1964;52:692-7.
8. Padbiri VS, Dandawate CN, Goverdhan MK. Chikungunya epidemic at Barsi: Preliminary epidemiological, virological and serological findings. Maharashtra Med J 1973;20:221-4.
9. Carey DE, Myers RM, DeRanitz CM, Jadhav M, Reuben R. The 1964 chikungunya epidemic at Vellore, South India, including observations on concurrent dengue. Trans R Soc Trop Med Hyg 1969;63:434-45.
10. Rodrigues FM, Patankar MR, Banerjee K, Bhatt PN, Goverdhan MK, Pavri KM, *et al.* Etiology of the 1965 epidemic of febrile illness in Nagpur city, Maharashtra State, India. Bull World Health Organ 1972;46:173-9.
11. Ravi V. Re-emergence of Chikungunya virus in India. Indian J Med Microbiol 2006;24:83-4.
12. Wadia RS. A neurotropic virus (chikungunya) and a neuropathic aminoacid (homocysteine). Ann Indian Acad Neurol 2007;10: 198-213.
13. Chatterjee SN, Chakravarti SK, Mitra AC, Sarkar JK. Virological investigation of cases with neurological complications during the outbreak of haemorrhagic fever in Calcutta. J Indian Med Assoc 1965;45:314-6.
14. Condon RJ, Rouse IL. Acute symptoms and sequelae of Ross River virus infection in South-Western Australia: A follow up study. Clin Diagn Virol 1995;3:273-84.
15. Selden SM, Cameron AS. Changing epidemiology of Ross River virus disease in South Australia. Med J Aust 1996;165:313-7.
16. Schuffenecker I, Iteman I, Michault A, Murri S, Frangeul L, Vaney MC, *et al.* Genome Microevolution of Chikungunya Viruses causing the Indian ocean out break. PLOS Medicine 2006;3e263.

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