RESEARCH PAPER

Encephalitic presentation of Neonatal Chikungunya: A Case Series

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Objective: To describe clinical features and early neurological outcomes in neonatal Chikungunya. **Methods**: Clinical, pathological and radiological details of neonates with acute encephalitic features and typical rash, later diagnosed as Chikungunya, are presented. Neurodevelopmental evaluation and imaging was done at discharge/three months. **Results**: Abnormal neurological examination with fever was typical presentation in all 13 babies with/without seizures/peri-oral rashes; 12 had persistent neurological abnormalities at discharge. A follow-up at three months revealed continued neurodevelopmental deficits. Neuroimaging abnormalities were seen in eight out of ten cases. **Conclusions**: Perinatal Chikungunya should be considered in neonates presenting within first week with fever, encephalopathy and perioral rashes with/without seizures with history of maternal Chikungunya within last week before delivery.

Keywords: *Acute encephalitis syndrome; Meningoencephalitis; Neonate; Rash*.

Chikungunya infection has seen a re-emergence in India [1]. Typically described as a disease of adult and pediatric population presenting with fever, arthralgia, arthritis, rash and constitutional symptoms [2]. It is rarely considered as a diagnosis in neonates, with little knowledge about natural history and clinical features. Neurotropism of Chikungunya is under-reported even in adults and children, and much rarely been described in neonates [3]. We describe clinical and laboratory features of neonates presenting with acute encephalitis syndrome and later diagnosed as Chikungunya infection.

METHODS

The medical record review was conducted in the neonatal intensive care unit of a tertiary-care center in Delhi. Babies who presented with neonatal sepsis like features (fever, lethargy, poor suck, feed intolerance, respiratory distress, jaundice, skin rash, seizures, shock, DIC *etc*.) but not supported by laboratory workup for bacterial sepsis/meningitis were worked up for Chikungunya in view of outbreak in the city (especially, in those with history of maternal fever). NIV CHIK IgM Capture Enzyme-linked immunosorbent assay (ELISA) (version 3, 4) was done in serum samples after obtaining consent from parents. CSF Reverse Transcriptase Polymerase Chain reaction (RT-PCR) was done from a reference laboratory. A large number of cases in a short period prompted us to plan their detailed neuro-developmental follow-up, and information about clinical features and laboratory investigations was compiled retrospectively from case records. Neurosonogram and MRI brain were done. Neurological examination was done using Hammersmith neonatal examination tool at discharge/at three months of age.

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A congenital Chickungunya case was defined as a baby born to mother with high grade fever within seven days before delivery with IgM seropositivity or CSF-positivity at time of neonatal diagnosis, or a symptomatic baby in first seven days of life having a positive IgM ELISA/RT-PCR in serum/CSF and negative bacteriological cultures. Any seropositivity or CSF-positivity found in a symptomatic baby not associated with maternal infection was defined as acquired Chikungunya.

RESULTS

Ninety nine babies were admitted between August and November, 2016, out of which 13 (11 males) were confirmed as Chikungunya. 10 cases were congenital, two acquired. One baby was adopted and maternal clinical and laboratory status were not known. Encephalopathy was present in all with duration varying from 10-15 days; 11 presented with fever and six presented with seizures (***Table* I**). Ten cases had a characteristic acrofacial hyperpigmentation beginning three to four days after fever in peri-oral region leading to characteristic 'brownie-nose pigmentation' **(*Fig.* 1)**, later

spreading to trunk and limbs in patchy fashion. Shock was present in two cases but was successfully treated and no death occurred. Hammersmith neonatal examination showed hypotonia in 12 out of 13 infants at discharge; visual and auditory development was normal in all 13 babies.

Neuro-developmental assessment at three months demonstrated four children with delayed milestones, out of which two cases each had hypotonia and hypertonia. Seven cases had normal tone and achieved normal milestones. Hyperpigmentation disappeared in all babies. One baby showed additional flexion deformity in bilateral thumbs and right middle finger at one month, which resolved by three months with the help of physiotherapy**.** Two babies were lost to follow-up.

CSF-RT-PCR could only be done in one neonate which was positive. CSF culture was sterile in all cases with cytology typical of viral meningoencephalitis. CSF was completely normal in one baby. Thrombocytopenia was present in 12 babies but none had clinical bleeding **(*Table* I**).

TABLE I CLINICAL AND LABORATORY FEATURES OF NEONATES WITH CHIKUNGUNIYA (*N*=13) [4]

Clinical features	*n*
Symptoms	
Lethargy	13
Fever	11
Feed refusal	13
Convulsions	6
Hyperpigmentation	10
Hypotonia	13
Investigations	
Leucopenia <6000/cumm	3
Thrombocytopenia <50,000/µL	12
CRP >1 mg%	6
Positive serum IgM (cases)	13
Positive serum IgM (Mother)	10
USG Cranium at discharge	13 normal
USG Cranium at 3 months, *n*=2	2 abnormal
MRI at 3 months, *n*=10	8 abnormal
OAE, *n*=12	12 normal
Cerebrospinal fluid Parameters	
Hypoglycorrhachia (<45 mg%)	9
Increased protein (>80 mg%)	9
Pleocytosis (>15 cells/mm^3)	2
Sterile culture	13

CRP=C-reactive protein, USG=ultrasonography; MRI=Magnetic resonance imaging; OAE=Otoacoustic emission.

MRI brain had evidence of white matter hyperintensities on T2 and FLAIR images involving frontal and parietal lobes in bilateral peri-ventricular and subcortical region with evidence of diffusion restriction in rostrum and splenium of corpus callosum in three patients. No post-contrast enhancement/hemorrhage or infra-tentorial/cerebellar involvement was seen.

Follow up MRI scan after three months revealed cystic encephalomalacia and ventricular dilatation in two cases, and diffuse cerebral atrophy in one **(*Fig*. 2).** Oto-acoustic emissions (OAE) screening was normal in 12 babies and abnormal in one at discharge, which normalized at three months.

DISCUSSION

A major finding in this study was that neonatal Chikungunya was quite common during the outbreak. Congenital infection was more frequent than acquired. A striking clinical feature was neurotropism, which was evident in all cases in form of refusal to feed, lethargy and seizures. Another common clinical finding was hyperpigmentation following a typical pattern. Laboratory features were conspicuous by thrombo-cytopenia and positive serum IgM Chikungunya. Initial USG cranium was normal in all cases but follow-up MRI scans were abnormal in majority, along with developmental delay in these cases.

The study had a few limitations as information was collected retrospectively and all cases were from referral unit which could have resulted in bias. No statistical tests could be performed due to small number of patients.

In our study, more male infants were admitted with the infection, similar to another Indian study [5]. Most cases were prenatally acquired similar to a data from the French Reunion islands [6]. In contract to the predominant encephalopathic presentation in this study, a Latin American study [7] showed only a 7.1% incidence of meningoencephalitis in newborns. However, review of

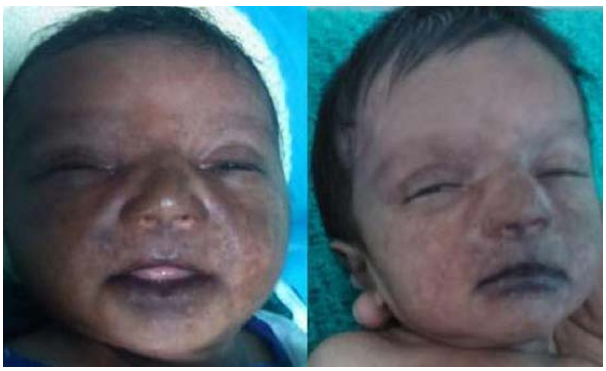


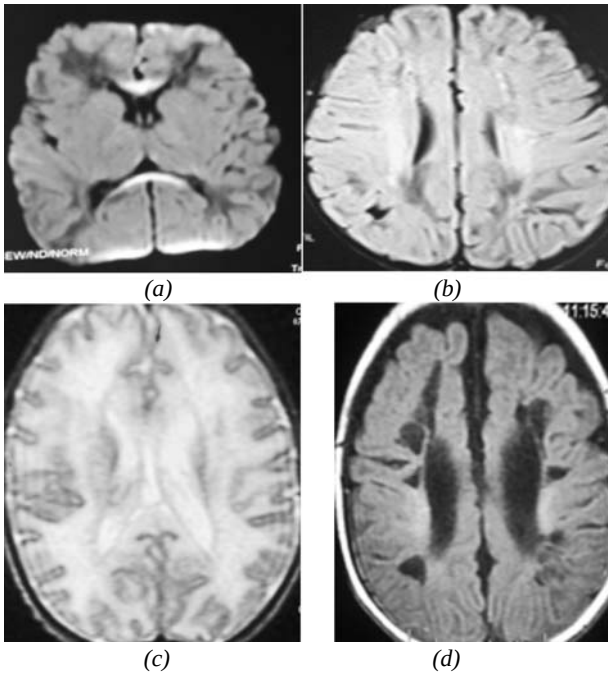
FIG. 1 *Acro-facial cutaneous hyperpigmentation.*

WHAT THIS STUDY ADDS?

- Neonatal Chikungunya should be considered in neonates presenting with fever, encephalopathy and cutaneous hyperpigmentation with/without seizures.
- Confirmed cases need a detailed neurodevelopmental follow-up.

their study shows that 98-100% babies presented with irritability and refusal to feed, which may suggest presence of encephalopathy. The cohort in this study was from intramural deliveries while ours were referred babies.

A higher incidence of encephalitis in neonates with Chikungunya could be attributed to greater viral replication and delayed clearance in infants [8]. Ineffective interferon-1 activation has been demonstrated in mice to be associated with severe disease. Neurological spread occurs through areas in brain poorly protected by blood brain barrier [9]. The plausible mechanisms of neuronal damage are: invasion of choroid plexus and leptomeninges leading to defective neuronal migration. Another possibility could be microglial activation [10]. The study on mice also demonstrated that the vertical transmission of the virus is Peri-partum and not ante-partum [9].



(a) *(b)* *(c)* *(d)*

FIG. 2*a* *and* ***2b:*** *MRI findings in a 15-day-old neonate with encephalopathy secondary to mother to child transmission of chikunguchikungunya virus infection: (a) Diffusion-weighted image showing hyperintense signal in corpus callosum; (b) FLAIR image showing hyperintensity in bilateral centrum semiovale.* ***2c*** *and* ***2d:*** *MRI findings in a 20-day-old neonate: (c) T2-weighted axial scan showing areas of hyperintensity in periventricular and frontoparietal white matter; (d) Follow-up scan after 3 months, FLAIR axial image showing altered signal intensity in bilateral deep white matter with cystic changes and dilated lateral ventricles.*

Similar radiologic and developmental findings were noticed in a cohort study from Reunion Island [10]. Peri-oral hyper pigmentation fever, leukopenia and mild thrombocytopenia were a predominant feature in our study, similar to another study [5], post-inflammatory hyperpigmentation could be due to virus-triggered increased intra-epidermal dispersion/retention of melanin [11]. Fixed flexion deformity in bilateral thumb reported in one of our babies is similar to another case-report [12].

Our study shows that Chikungunya should be considered as a differential diagnosis in neonates presenting with fever, typical hyperpigmentation and encephalopathy especially during outbreaks. Cases with perinatal infection are prone to developmental delay and require long term neuro-developmental follow-up.

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