

Clinical profile and neuroimaging of neonates with influenza encephalopathy

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ABSTRACT

Background: Pediatric influenza is found primarily in children under 5 years of age, and it is very difficult to distinguish the illness caused by influenza, a virus infection based on the signs alone. **Objective:** The objective of this study is to analyze the clinical profile and neuroimaging of neonates admitted with seizures followed by encephalopathy. **Methods:** A descriptive study was conducted among neonates admitted to our neonatal intensive care unit, with neurological manifestations such as poor feeding, lethargy followed by seizures and poor sensorium in the 1st week of life. During the study period, 14 neonates were included with similar neurological manifestations. **Results:** Our study neonates had poor feeding and lethargy (57.1%) before the onset of seizures. The mean day of the onset of seizure was day 4, and the mean duration of encephalopathy lasted for 63 h. We could detect influenza A in cerebrospinal fluid-polymerase chain reaction only in two neonates and H1N1 influenza in one neonate, but all our study neonates had consistent findings on the magnetic resonance imaging (MRI) brain suggestive of viral infection probably influenza A as its circulation in the community is considered common. The mean day of discharge from the hospital was 11.5 days. At discharge, all neonates were on breastfeeds and had no focal neurological deficit. **Conclusions:** The possibility of influenza A-related encephalopathy should be considered as a differential diagnosis if a neonate presents with poor feeding, lethargy followed by seizures and encephalopathy in the 1st week of life and their brain MRI–diffusion-weighted imaging shows a periventricular white matter involvement.

Key words: *Influenza A, Neonatal encephalopathy, Neonates, Viral encephalopathy*

Influenza A is a viral infection that affects the general population but very old and the very young population are especially affected. Pediatric influenza is found primarily in children under 5 years of age. The symptoms of influenza A are non-specific below 2 years of age, and it is only from the age of 4–5 years that its clinical manifestations can guide us toward the disease [1].

Less frequently, newborn infants present with typical signs of influenza, such as a cough and fever. Influenza or its complications in newborn infants may manifest as apnea, low-grade fever, fast breathing, cyanosis, excessive sleeping, lethargy, and poor feeding [2]. In newborn infants, it is difficult to distinguish illness caused by influenza A virus infection based on the signs alone. Delay in identifying the cause of respiratory illness in newborn infants can lead to additional complications, and therefore, the differential diagnosis should include influenza virus infection where its circulation in the community is known [2].

The best way to diagnose influenza is through the detection of viral RNA by reverse-transcriptase polymerase chain reaction (RT-PCR) or by viral culture from upper respiratory tract specimens collected as close to illness onset as possible [3]. Serologic testing (antibody detection) is not recommended for routine diagnosis. Preferred respiratory samples for influenza

testing include nasopharyngeal or nasal swab and nasal wash or aspirate [4].

Influenza-related neurological complications in children are well described in literature. Neurological complications were more likely to occur with pandemic influenza than seasonal influenza. Pediatric influenza A H1N1 encephalopathy presenting as seizures and altered mental status and abnormal electroencephalograph (EEG) findings have been reported during 2009 pandemic influenza A H1N1 seasons from India [5]. Literature has also reported the detection of the H3N2 strain of influenza A among neonates of 5–9 days old [6], suffering with respiratory illness.

Neurotropic pathogens can access the brain by various routes including retrograde axonal transport along motor and olfactory neurons and hematogenous spread across the blood–brain barrier (BBB), blood – cerebrospinal fluid (CSF) barrier, and meningeal–CSF barrier, through direct infection of endothelial cells or through spread of infected leukocytes across the BBB into the brain parenchyma [7].

Pathological examination of the brain in influenza virus-associated encephalopathy suggests that direct viral invasion or inflammation is not involved in the pathogenesis, but that vascular inflammation has an important role as it leads to apoptosis of the

vascular endothelium and also the brain. Lack of integrity of the cerebrovascular vessels allows seepage of plasma into the brain parenchyma, which causes cerebral edema and triggers brain apoptosis [8,9]. However, the neurological manifestations and the pathological findings of the brain in influenza-related neonatal encephalopathy are not reported in literature. Hence, the present study was conducted to analyze the clinical profile and neuroimaging of neonates admitted with seizures and encephalopathy.

METHODS

This descriptive study was conducted in a tertiary care center, located in Kerala, South India, from February 2017 to October 2017. The study was approved by the Institutional Ethical Committee. Informed written consent was obtained from parents of all subjects before enrolment in the study. In this study, neonates admitted to our neonatal intensive care unit (NICU), with neurological manifestations such as poor feeding, lethargy followed by seizures, and poor sensorium in the 1st week of life were included for analysis.

Based on the past 8 months' admission rate in our hospital, a convenient sample size of 14 neonates delivered in the hospital during the study period was selected. Neonates with neurological manifestations and magnetic resonance imaging (MRI) brain-diffusion-weighted imaging (DWI) findings consistent with viral infection were included in the study. Encephalopathy was defined as absent/weak Moro reflex, absent/poor suck, weak cry, reduced spontaneous movements, and poor response to touch.

All neonates with the neurological manifestations at admission were subjected to laboratory investigations such as serum electrolytes, blood sugar, sepsis screening, blood culture, CSF analysis, and CSF culture. Furthermore, CSF for real-time RT-PCR for neurotropic viruses (viral panel selection as per laboratory) was sent to Public Health Laboratory and Rajiv Gandhi Centre for Biotechnology, Trivandrum. Baseline metabolic screening (serum ammonia, arterial blood gas, and urine ketones) and transcranial magnetic stimulation/multiple sclerosis were done for all babies, as the initial clinical picture was difficult to differentiate from an inborn error of metabolism. Once baby became seizure free for 2–3 days, EEG and MRI brain were done before the discharge from the hospital. MRI brain was interpreted by chief radiologists, working in a tertiary care center for more than 10 years, and had received training in interpreting the neonatal brain MRI.

Empirical intravenous (IV) antibiotics and IV acyclovir were initiated from day 1 of seizure considering the possibility of meningitis/herpes simplex virus encephalitis, as the clinical picture of bacterial/viral infection was difficult to differentiate at the time of admission. In our unit, we consider starting IV acyclovir in neonates with seizures whose CSF analysis was negative for bacterial infection and IV acyclovir was stopped with the availability of CSF viral PCR reports. IV anticonvulsants were used to control the seizure activity, and other supportive

management was done as per the unit policy. Babies were discharged when there was no focal neurological deficit and they were on direct breastfeeds. We have planned for follow-up of these babies at the 18 months' age for neurodevelopmental assessment and repeat brain MRI.

The clinical profile, laboratory investigations, and the neuroimaging findings were collected from medical records and entered in the Microsoft Excel sheet for analysis, and the results were expressed in terms of mean, standard deviations, and percentage.

RESULTS

In this descriptive study, a total of 14 neonates admitted with seizures (multifocal clonic) and encephalopathy were included in the study. We had 11 (78.6%) term and 3 (21.4%) late preterm neonates. Mean gestation was 37.3±1.1 weeks, and the mean birth weight was 2800±400 g. One neonate among the late preterm group required bag and mask resuscitation at birth but had normal sensorium after 1 h of life. Two neonates among the late preterm group had a maternal risk of sepsis (preterm prelabor rupture of membranes). Among the study group, 11 neonates were boys (78.6%) with a sex ratio of 3.6:1. We could not find a definite history of respiratory illness in mothers or among caregivers to find the possible source of infection.

Except for one neonate, all neonates were transferred from postnatal ward to NICU with a history of seizures. Before the onset of seizures, eight neonates (57.1%) had poor feeding and lethargy, weak cry in three neonates (21.4%), and fever in one (7.1%) neonate. The onset of seizure in most of the babies was on day 4 (78.6%) (Table 1). All the 14 neonates had either 2 or more signs of encephalopathy (i.e., absent/weak Moro reflex, absent/poor suck, weak cry, reduced spontaneous movements, and poor response to touch).

We could send CSF-PCR for neurotropic viruses only in 9 neonates of 14 neonates. Of these, CSF-PCR was positive for influenza A in two neonates and H1N1 in one neonate, and it was negative in rest of the sic neonates. Other laboratory investigations were normal in all neonates. Sepsis screening was negative; except one neonate who had elevated CSF protein, all other neonates had normal CSF cell counts, glucose level, and protein level; blood and CSF culture showed no growth. Baseline metabolic screening was also found to be in the normal range for all the study neonates.

MRI brain (Fig. 1) has shown periventricular white matter hyperintensities in the DWI, which was consistent in all 14 neonates admitted with seizures suggestive of viral infection,

Table 1: Day of onset of seizures

| Postnatal day | Number of babies (%) |
|---------------|----------------------|
| Day 2 | 1 (7.1) |
| Day 4 | 11 (78.6) |
| Day 5 | 1 (7.1) |
| Day 6 | 1 (7.1) |

probably influenza A, as this virus circulation in the community is considered to be common. MRI brain DWI of a neonate with negative CSF-PCR showed bilateral, symmetrical, periventricular, subcortical hyperintensities in the frontal, parietal, temporal, and occipital lobes, genu, body, and splenium of corpus callosum, cerebral peduncles, posterior thalamus, anterior midbrain, and internal and external capsule (Fig. 2). No congenital malformations of the brain were detected among the study neonates. Abnormal EEG findings were found in 4 neonates showing slow and spike-wave discharges (Fig. 3).

All neonates were treated with IV antibiotics and started on IV acyclovir as CSF analysis was negative for bacterial infection and IV acyclovir was stopped with the availability of CSF viral PCR reports. One neonate with H1N1 influenza A virus received oseltamivir orally for 5 days. All babies showed a response to supportive treatment and their sensorium improved after 48–96 h (mean 63 h) of encephalopathy. All babies were discharged in the 2nd week of life with no focal neurological deficit and were on direct breastfeeds with the mean duration of hospital stay of 11.5 ± 1.6 days.

DISCUSSION

Influenza A-related neurological complications in children are well described in literature. During pandemic H1N1 influenza 2009–2010, a very few reports were there on influenza A H1N1 infection among neonates [10]. However, till now, no studies on neonatal encephalopathy related to influenza A infection are being reported. Neonates, due to the immaturity of their immune system, could be at high risk for the development of severe illness and lethal outcome. Although studies have not shown sex predilection for influenza A infection-associated encephalopathy, in our study, we could find a sex ratio of 3.6:1 among boys:girls.

Literature has reported seizures with or without encephalopathy as a neurologic complication associated with influenza in children. Febrile seizures have been reported in up to 20% of children aged 6 months through 5 years hospitalized with influenza [11,12]. Most of the case series came from Japan, Taiwan, and Korea during the influenza epidemic which suggests that the disease could be more common in these areas, although there is no clear explanation for a geographic predisposition. The cases of encephalopathy in Japan have been described as severe, with a high fatality rate among children [13–15]. However, no case report on influenza-related neonatal encephalopathy is reported in literature.

Poehling *et al.* [2] stated that influenza A in newborn infants may manifest as apnea, low-grade fever, fast breathing, cyanosis, excessive sleeping, lethargy, and poor feeding. Our study analysis showed neonates presented as poor feeding and lethargy preceding the onset of seizures in 57.1% of our cases. A weak cry was found in three neonates (27.4%) and fever in one neonate (7.1%). Mean day of onset of seizure was day 4 (78.6%).

Studies have shown that although most patients with influenza-associated seizures do not have abnormalities on the EEG or neuroimaging [16,17], those with EEG abnormalities

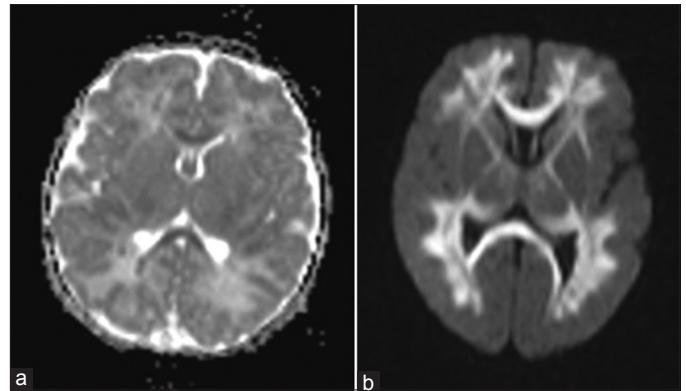


Figure 1: (a and b) Magnetic resonance imaging brain–diffusion-weighted imaging of a neonate with cerebrospinal fluid–polymerase chain reaction positive for influenza A virus showing bilateral, symmetrical, periventricular white matter hyperintensities in both cerebral hemispheres

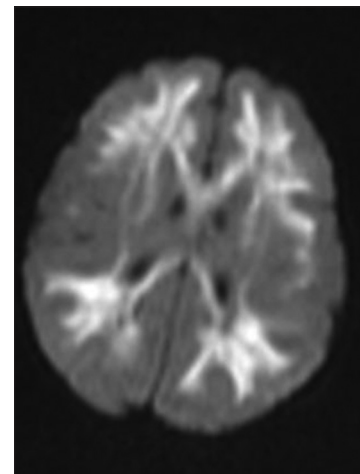


Figure 2: Magnetic resonance imaging brain–diffusion-weighted imaging of a neonate with cerebrospinal fluid–polymerase chain reaction negative for neurotropic viruses

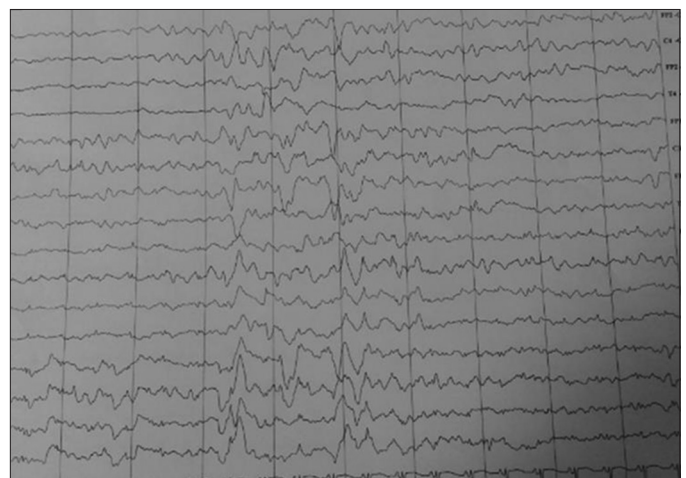


Figure 3: Electroencephalograph showed bilateral independent slow and sharp wave discharges

may have diffuse slowing, spike and wave discharges, or a burst suppression pattern [17]. In our study, we had abnormal EEG in four neonates showing slow and spike-wave discharges.

The MRI brain has shown periventricular white matter

hyperintensities in the DWI, which was consistent in all 14 neonates admitted with seizures suggestive of viral infection, probably influenza A, as this virus circulation in the community is considered to be common. Studies have shown that there have been attempts to separate encephalopathy from encephalitis based on the presence of central nervous system inflammation. Unfortunately, only a few patients with influenza-associated encephalopathy had elevated protein or mild pleocytosis in the CSF; in most cases, CSF was normal [13,14].

In our study, except one neonate who had elevated CSF protein, all other neonates had normal CSF cell counts, glucose level, and protein level. As CSF analysis findings are often unremarkable in neonates with influenza-associated encephalopathy, the final diagnosis is based on clinical assessment of the neurologic manifestations and laboratory confirmation of acute influenza virus infection [18].

We could send CSF viral PCR for 9 neonates of 14 neonates. However, we could detect influenza A virus only in two neonates in the CSF by reverse PCR and detected H1N1 influenza virus in the CSF in one neonate. Although six neonates had negative CSF viral PCR, the MRI brain–DWI and the clinical assessment of neurological manifestations were similar in all 14 neonates. In most case reports, patients with influenza-associated seizures survived with no residual neurologic sequelae [12,16,19,20]. In our study also, all neonates regained normal sensorium and had no focal neurological sequelae at discharge. Since this was a hospital-based study, the sample size was small, so further studies on larger sample size is essential for better results.

CONCLUSION

This study highlights the possibility of influenza A-related encephalopathy as a differential diagnosis, if a neonate presents with poor feeding and lethargy followed by seizures and encephalopathy in the 1st week of life, and their brain MRI–DWI shows a periventricular white matter involvement. Furthermore, authors suggest that more similar studies should be conducted among neonates to make a definite diagnosis of neonatal influenza A encephalopathy.

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Jemila James wrote the article, performed the data collection and analysis of data, and prepared the manuscript, Roshan Joseph John helped in collecting data and neuroimages, Arun Edwin involved in patient care of study neonates, and Lalitha Kailas and PMC supervised and helped in editing the manuscript. All authors approved the final manuscript.

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