Short Communication

Clinical characteristics of neurological manifestations in influenza-A (H1N1) among children in a tertiary care hospital, South India, during 2019

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ABSTRACT

Objective: The objective of the study was to study the neurological manifestations of influenza-A in children. **Materials and Methods:** This retrospective study was conducted in a tertiary care hospital in South India during the seasonal epidemic of flu in 2019. All children aged 1 month–12 years with evidence of neurological manifestations and positive nasopharyngeal swab for influenza A were evaluated for the clinical features, treatment, and outcome. **Results:** Sixteen patients had neurological manifestations and 44% of them were <2 years of age. The most common manifestations in this cohort was altered sensorium (87.5%) followed by seizures (62.5%). Fourteen patients developed symptoms within 5 days of onset. Only two children had cerebrospinal fluid pleocytosis and five children had abnormal neuroimaging findings. Intensive care management was required for 81% of children and the cause specific mortality was 18.75%. **Conclusion:** Neurological manifestation in influenza-A should be considered in children during epidemics and intensive care management can go a long way in improving the survival rates.

Key words: H1N1, Influenza A, Neurological manifestations

The novel influenza-A (H1N1) was first reported in Mexico and the South USA in 2009. The virus then quickly spreads worldwide, demonstrating efficient human-to-human transmission [1]. The pandemic started in India in the month of August 2009 and the index cases were reported from Pune. Soon the epidemic spreads itself to other parts of the country. H1N1 influenza-A 2009 pandemic strain is now responsible for periodic seasonal outbreaks of influenza in India.

The most infections with the novel influenza-A (H1N1) have resulted in self-limiting, uncomplicated disease. The seasonal influenza virus infection has been associated with various neurological complications, mostly accompanied with cases of encephalitis and encephalopathy. There are very few reports about the neurological complications of influenza-A H1N1 virus in literature and the prevalence of these complications has not been evaluated yet. Reports from India pertaining to the neurological manifestations of H1N1 are limited to two case reports and a recent case series [2-4]. The present analysis is our experience from a tertiary care referral institute in South India admitting influenza-A cases with special reference to the neurological manifestation from July through August 2019.

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MATERIALS AND METHODS

We retrospectively identified children aged from 1 month to 12 years with evidence of seasonal influenza-A and associated neurological symptoms admitted in a tertiary care teaching hospital in South India during July-August 2019. A confirmed case of seasonal influenza-A was defined as an individual with an influenza-like illness (ILI) with laboratory-confirmed influenza-A virus detected by reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swab. ILI was defined as fever (temperature of 100°F [37.8°C] or greater) with cough or sore throat in the absence of a known cause other than influenza.

Eligible patients are identified and their case records are analyzed to collect demographic profile, clinical symptoms, neurological and other systemic findings, investigations results, lumbar puncture results, neuroimaging report, treatment given, and outcome. RT-PCR in the nasopharyngeal swab specimen was done based on the standard protocol in the accredited laboratory, brain magnetic resonance imaging (MRI) and computed tomography scan were done wherever required and reported by a neuroradiologist who had knowledge about patient's clinical condition. Lumbar puncture was done in all patients and cerebrospinal fluid (CSF) study was done in the same laboratory.

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Ethical clearance was obtained from the Institutional Ethical Committee.

RESULTS

Sixteen patients with influenza-related neurological manifestations were enrolled in the study. The median age of the cohort was 3 years 6 months and the range was from 1 year to 9 years. In the cohort, 44% of the affected children were <2 years. The male-to-female ratio in the cohort was 1.2:1. About half of the children had associated comorbidities such as developmental delay in 3, Dravet syndrome in 1, recurrent febrile seizures in 1, and bronchial asthma on prophylaxis in 3. PCR assays on nasopharyngeal swab detected influenza-A in all patients, with H1N1 subtype found in 13 cases (81%) and H3N2 in one child and non-typable in two.

Eight patients (50%) developed neurological symptoms within 24 h of onset of illness whereas six patients developed within 1–5 days and two patients after 5 days of illness. The most common neurological manifestation seen in this cohort was altered sensorium in 14 patients (87.5%). Ten patients had seizures (62.5%) of which two patients presented with status epileptics and one had focal seizure. Other symptoms such as headache, vomiting, and hypertension were present in 4 children (25%) suggesting raised intracranial pressure.

In addition to neurological manifestations, the affected children had other multisystem involvement as well. Elevated transaminases were present in 10 children (62.5%), hyponatremia in 10 (62.5%), shock requiring ionotropic support in 7 (43.75%), acute respiratory distress syndrome (ARDS) in 5 cases (31.25%), acute kidney injury in 3 (18.75%), myocarditis in 1 (6.25%), and coagulopathy in 1 case (6.25%).

CSF analysis was done in 13 patients and 3 patients showed abnormalities (23%). One child had CSF pleocytosis (all lymphocytes) and one child had elevated protein (more than 40 mg/dl) and one child had both. All three patients with abnormal CSF findings showed some abnormality in MRI also. H1N1 was demonstrated in CSF by PCR in two patients.

Neuroimaging (MRI brain) was done in eight patients and four patients showed some abnormality. Two patients had features of demyelination in the cerebral cortex and hyperintensity in basal ganglia, thalami, and pons. There was also diffusion restriction in these areas suggestive of acute disseminated encephalomyelitis (Fig. 1). One patient had isolated cytotoxic lesion of the splenium of corpus callosum which is a specific feature of influenza A (mild encephalitis/encephalopathy with reversible splenial lesion – MERS) (Fig. 2). One patient had features of early hydrocephalus.

Pediatric intensive care admission was required in 13 patients. The mean duration of pediatric intensive care unit stay among survivors was 8 days (1–35 days). The total duration of hospital stay was 7–42 days. Seven patients needed inotropic support and five patients required mechanical ventilation. The duration of mechanical ventilation in five patients was 1–8 days (mean 3.6 days). All patients received appropriate doses of oseltamivir for 5 days. Three patients died due to multiorgan dysfunction and the mortality rate is 18.75%. Among children with existing neurological problems (four cases), one child expired and rest three children had some deterioration. Ten children recovered completely without any neurological deficit.

DISCUSSION

Influenza infection can lead to a variety of neurologic complications as influenza-associated encephalitis or encephalopathy (IAE), which is more frequently noted in pediatric populations. In our study, majority of children who were affected with neurological manifestations were <2 years and this observation is similar to the existing literature [5]. Our study shows that 50% of children had comorbidity or preexisting disease, especially neurodevelopmental disorder (five cases). Children with neurological disorders and other chronic conditions represents a significant fraction of patients hospitalized and developing complications worldwide and vaccination is specifically recommended for this group of children [6]. Our case series showed that 80% of cases were attributed to HINI. Similar to our results, other investigators also have reported that neurological complications are more commonly associated with H1N1 [7,8]. Epidemiological transmission and increased propensity of H1N1 to cause neurological complications could explain the virological distribution in our case series.

Neurological symptoms developed within 5 days in 87% of patents which is comparable to a study by Amin *et al*. where 65% developed symptoms within 5 days [9]. Similar to other studies in the literature, most common neurological manifestations of influenza-A was altered sensorium and seizures [4,7-9]. The neurological manifestation of influenza is due to the direct invasion of the virus to the central nervous system, associated metabolic encephalopathy associated with infection, and immune dysregulation due to the viral infection [10].

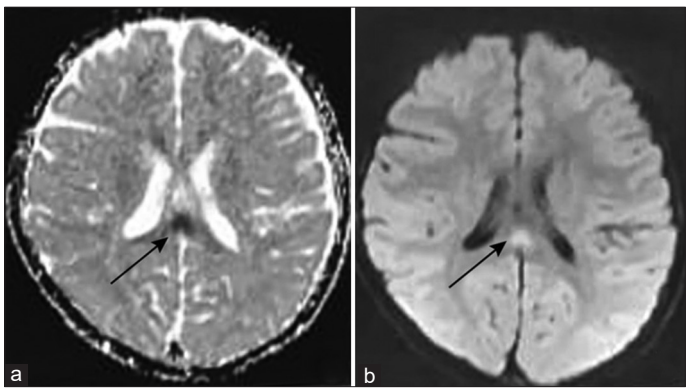

Figure 1: (a) ADC image with low apparent diffusion in splenium. (b) Diffusion restriction in splenium of corpus callosum (CLOCCs)

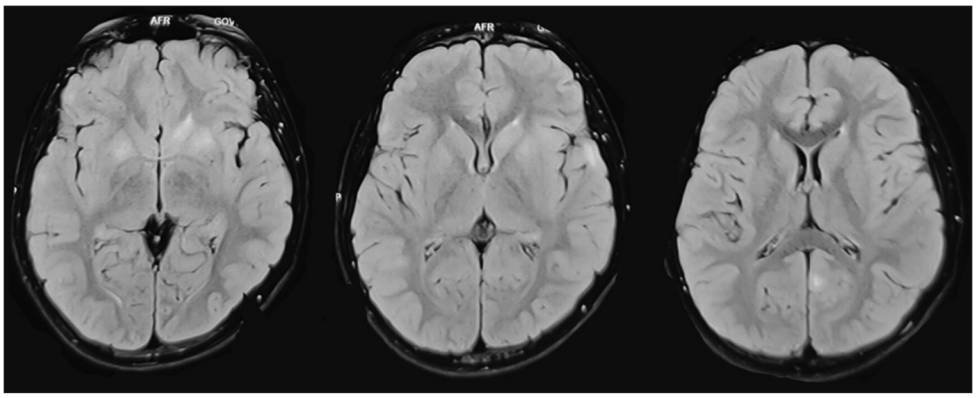

Figure 2: T2 FLAIR image shows hyperintensities in bilateral cerebral cortex (left more than right) and basal ganglia

CSF analysis performed showed pleocytosis and elevated protein only in three patients. The previous studies reported a low rate of CSF pleocytosis in most of the patients with clinical and neuroradiological evidence of central nervous system involvement [7,8,11]. This suggests that nervous system involvement in most cases may be due to inflammatory mediated. IAE is a rapidly progressive encephalopathy primarily characterized by an impaired level of consciousness developing within a few days of influenza infection. A number of distinct clinical syndromes have been categorized under the umbrella category of IAE including acute necrotizing encephalopathy, acute encephalopathy with biphasic seizures with late reduced diffusion, and MERS [12]. Three of our cases had characteristic MRI abnormalities.

The outcome of neurological complications in influenza-A is highly variable ranging from a self-limiting illness to severe complications. The mortality in the literature varies from 4% to 30%. Mortality rate in our case series was 18.75%, which is comparable to other studies [13]. Pediatric intensive care management was required in 81% of our patients which is comparable with the literature [11,14]. In the absence of randomized control studies, with available literature, all our patients were treated with oral oseltamivir for 5 days. It has been shown that the treatment of influenza A-infected patients with neuraminidase inhibitors (oseltamivir and zanamivir) leads to reduction in duration of illness, hospital stay, complications, and mortality [15].

Our study presents several limitations. Primarily, it is a single-center study in a tertiary care hospital and collection of data was retrospective. Hence, this analysis may not reflect the actual distribution of the cases at the population level. Further community-based studies are required to analyze the actual neurological impact of H1N1 infection in the community. Radiological evaluation was not possible in all patients due to logistic reasons which may have affected the outcome of our study. If we had a long-term follow-up and outcome evaluation, it would be more meaningful with regard to the neurological manifestations.

CONCLUSION

Neurological manifestations can occur in influenza A (HINI) and the symptoms develop in majority during the first 5 days of illness. The most common symptom in this cohort was altered sensorium. Although CSF abnormality is not a very common feature, the virus can be demonstrated in some cases in CSF. Multiorgan dysfunction and intensive care management are required in most cases and the cause-specific mortality is 18.75%. In our cohort, there were no neurological sequelae in the children who recovered.

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