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Assessment of Influenza Associated Neurological Diseases in Children

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Abstract

Background: To assess influenza associated neurological diseases in children. **Materials & Methods:** One hundred twenty- eight children age ranged 2 months to 14 years with influenza and associated neurological disease of both genders were selected. Parameters such as length of stay, complete blood count, CSF biochemistry and clinical features were recorded. **Results:** The mean time between flu-like symptoms and neurological manifestations was 1.2 days, duration of hospitalization was 9.2 days. Clinical presentation at admission was fever seen in 120, neurologic manifestations were seizures in 84, altered consciousness in96, ataxia in 52 and respiratory manifestations were cough in 34 and dyspnea in 67. Complications were acute necrotizing encephalitis (ANE) in 68, hemorrhagic shock in 34 and mild encephalopathy with reversible splenial lesions (MERS) in 26. A significant difference was observed (P< 0.05). **Conclusion:** All children with acute neurological features during influenza season should be assessed for influenza-associated CNS complications. Most common complication was acute necrotizing encephalitis.

Keywords:- Acute necrotizing encephalitis, Hemorrhagic shock, Influenza, Neurological diseases.

INTRODUCTION

Influenza has long been associated with protean neurological manifestations. Neurological manifestations are an important complication of influenza infection. A wide variety of acute neurological presentations are reported, of which febrile seizures and encephalopathy are the most common, and approximately three-quarters of cases occur in children. Glaser et al,[1] reported an incidence of severe influenza-associated neurologic complications of 1.2 per 1 000 000 cases of H1N1pdm09 infection in California. Among hospitalized influenza cohorts, the proportion with influenza-associated neurological disease (IAND) ranges from 6% to 19%.

Influenza typically presents with respiratory symptoms. However, other organs such as gut, liver, and central nervous system may also be affected.[2] The burden of Influenza Associated Neurological Diseases (IAND) is higher in pediatric population as compared to adults, with children accounting for 73% and 84% of IAND cases in American and British series, respectively. The neurological symptoms typically occur within 14 days of onset of respiratory symptoms.[3]

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Neurological syndromes associated with influenza include seizures, meningitis, transverse myelitis, acute disseminated encephalomyelitis, Guillain-Barré syndrome, and encephalopathy/encephalitis.[4] These neurological manifestations occur most frequently in children. Signs/symptoms of influenza infection usually include fever, headache, cough, sore throat, myalgia and sometimes diarrhea and vomiting. The infection is usually self-limiting, although children, elderly people, immunocompromised patients and pregnant women have a higher risk of complications.[5] Central nervous system (CNS) involvement is rare, but is an important complication of influenza infection with approximatively three-quarters of cases regarding children. Neurological complications are reported to occur in 1–15% of influenza cases in the pediatric age, often self-resolving, although permanent sequelae or death can occur.[6] There are several challenges faced in treating such patients. Earlier stages of encephalopathy are difficult to pick in young children. Standardized tools such as Cornell Assessment for Pediatric Delirium may help in early identification. Risk factors for neurological involvement include age of 2–4 years and underlying neurological disease.[7] Considering this, the present study was undertaken with the aim to assess influenza associated neurological diseases in children.

MATERIALS & METHODS

One hundred twenty- eight children age ranged 2 months to 14 years with influenza and associated neurological disease of both genders were selected in this study. Children in which hospital admission was not required and when an alternative cause could better explain neurological manifestations were excluded. Institutional review and ethical committee approved that study. All parents were made aware of the study and the study was commenced after they agreed to give their written consent.

Demographic data of each children were recorded. Proven influenza infection was defined as positive polymerase chain reaction (PCR) for influenza RNA from throat or nasal swab, respiratory secretions, serum, or cerebrospinal fluid (CSF).Parameters such as length of stay, complete blood count, and CSF biochemistry was performed. Clinical features were also recorded. Results of the present study after recording all relevant data were subjected for statistical inferences using chi- square test. The level of significance was significant if p value is below 0.05 and highly significant if it is less than 0.01.

RESULTS

Maximum cases were seen in age group 5-7 years (boys- 30, girls- 25) followed by 8-14 years (boys- 24, girls- 17) and 2- 24 months (boys- 18, girls- 14). [Table 1].

The mean time between flu-like symptoms and neurological manifestations was 1.2 days, duration of hospitalization was 9.2 days. Clinical presentation at admission was fever seen in 120, neurologic manifestations were seizures in 84, altered consciousness in 96, ataxia in 52 and respiratory manifestations were cough in 34 and dyspnea in 67. Complications were acute necrotizing encephalitis (ANE) in 68, hemorrhagic shock in 34 and mild encephalopathy with reversible splenial lesions (MERS) in 26. A significant difference was observed ($P< 0.05$). [Table 2, Figure 1].

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Table 1: Distribution of children

Age groups	Boy	Girl	Total
2- 24 months	18	14	32
2- 7 years	30	25	55
8-14 years	24	17	41
Total	72 (56.3%)	56 (43.7%)	128 (100%)

Table 2: Clinical characteristic of patients

Variables	Parameters	Mean	P value
Time between flu-like symptoms and neurological manifestations (Days)		1.2	-
Duration of hospitalization (Days)		9.2	-
Clinical presentation at admission	Fever	120	Significant <0.05
Neurologic manifestations	Seizures	84	
	Altered consciousness	96	
	Ataxia	52	
Respiratory manifestations	Cough	34	
	Dyspnea	67	
Complications	Acute Necrotizing Encephalitis (ANE)	68	Significant <0.05
	Hemorrhagic Shock	34	
	Mild encephalopathy with Reversible Splenial Lesions (MERS)	26	

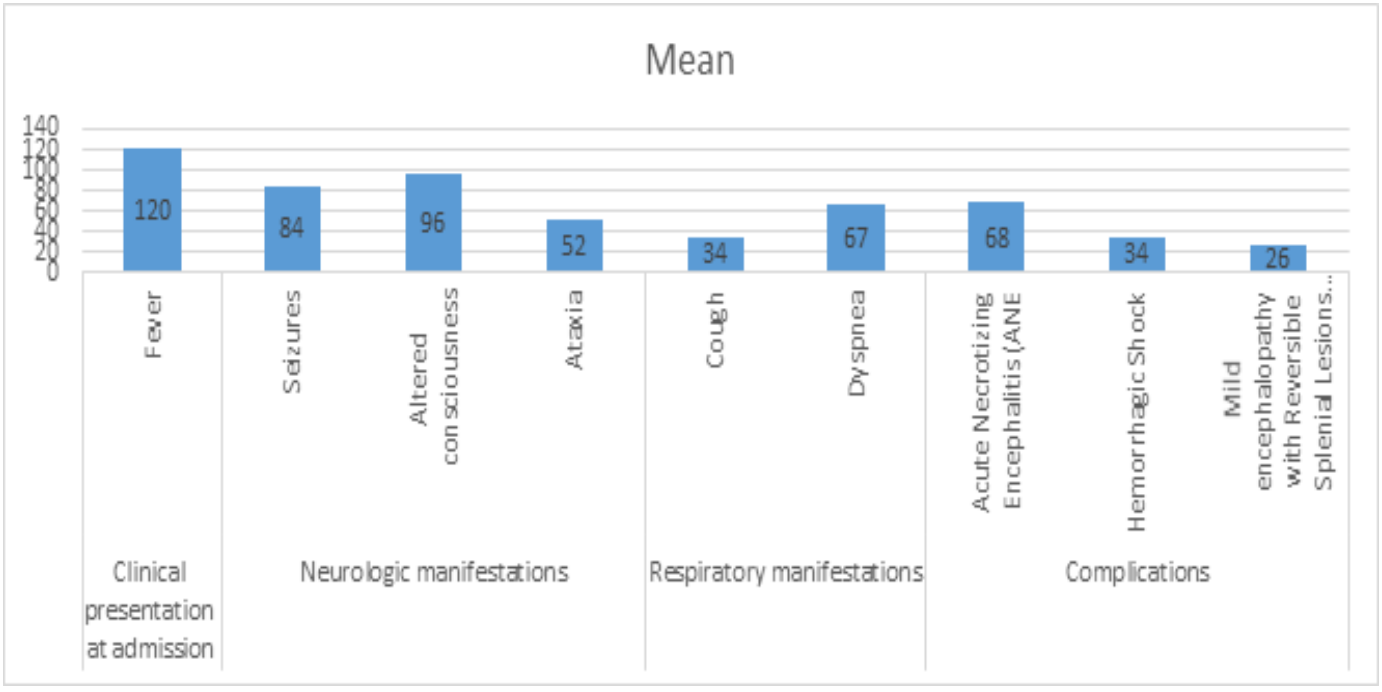

Figure 1: Clinical characteristic of patients

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Table 3: Blood laboratory findings

Laboratory findings	Mean
Leucocyte count (/mm3)	8024
Platelet count (/mm3)	290,000
Neutrophil count (/mm3	6028
Lymphocyte count (/mm3)	1374
Sodium (mEq/L)	134.2
CRP (mg/dL)	1.82
ALT (U/L)	26.2
Procalcitonin (ng/mL)	1.4

Leucocyte count (/mm3) count found to be 8024, platelet count (/mm3) was 290,000, neutrophil count (/mm3) was 6028, lymphocyte count (/mm3) was 1374, sodium (mEq/L) level was 134.2, CRP (mg/dL) level was 1.82, ALT (U/L) level was 26.2 and Procalcitonin (ng/mL) level was 1.4.

DISCUSSION

Influenza primarily affects the respiratory system and represents one of the most frequent causes of acute upper respiratory tract infections during the winter season.[8] The neurological disease is often defined noted as influenza-associated encephalitis/encephalopathy (IAE).[9] The term encephalopathy is preferred because influenza virus is rarely neuro-invasive, although a small number of published cases have been described with detection of influenza virus RNA in the cerebrospinal fluid (CSF) by means of molecular methods.[10] Neurological sign/symptoms attributed to influenza range from a mildly altered mental state, vertigo and brief febrile seizures to life threatening complications such as status epilepticus, meningitis, stroke, and demyelinating disease.[11]

There are several challenges faced in treating such patients. Earlier stages of encephalopathy are difficult to pick in young children. Standardized tools such as Cornell Assessment for Pediatric Delirium may help in early identification. Risk factors for neurological involvement include age of 2–4 years and underlying neurological disease.[12] Treatment options in IAND are limited to Oseltamivir and supportive care. Role of new antivirals such as Peramivir, Baloxavir in IAND is not defined. Steroids have been recommended in patients of ANE without brainstem lesions and a recent study suggests Tocilizumab as an add-on therapy in ANE. Another evolving aspect is role of biomarkers such as IL-6 and Cytochrome-c for IAND.[13] The present study assess influenza associated neurological diseases in children.

In our study, maximum cases were seen in age group 5-7 years (boys- 30, girls- 25) followed by 8-14 years (boys- 24, girls- 17) and 2- 24 months (boys- 18, girls- 14). Goenka et al,[14] determined neurological manifestations of influenza in twenty-five cases. 21 (84%) were in children and 4 (16%) in adults. Six (29%) children had pre-existing neurological disorders. Polymerase chain reaction of respiratory secretions identified influenza A in 21 (81%; 20 of which [95%] were H1N1) and influenza B in 4 (15%). Twelve children had encephalopathy (1 with movement disorder), 8 had encephalitis, and 1 had meningoencephalitis. Two adults had encephalopathy with movement disorder, 1 had encephalitis, and 1 had Guillain-Barré syndrome. Seven individuals (6 children) had specific acute encephalopathy syndromes (4

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acute necrotizing encephalopathy, 1 acute infantile encephalopathy predominantly affecting the frontal lobes, 1 hemorrhagic shock and encephalopathy, 1 acute hemorrhagicleukoencephalopathy). Twenty (80%) required intensive care, 17 (68%) had poor outcome, and 4 (16%) died.

Our study showed that mean time between flu-like symptoms and neurological manifestations was 1.2 days, duration of hospitalization was 9.2 days. Britton et al,[15] identified 54 cases of IAND at 2 tertiary children's hospitals from Australia that accounted for 7.6% of hospitalized influenza. These included 10 cases of IAE (1.4% hospitalized influenza). The mean annual incidence of IAE among Australian children (aged ≤14 years) was 2.8 per 1 000 000. The spectrum of IAND was broad and included IAE (n = 10) including distinct acute encephalopathy syndromes, simple febrile seizures (n = 14), other seizures (n = 16), acute ataxia (n = 4), and other subacute syndromes (transverse myelitis [n = 1], opsoclonus myoclonus [n = 1]). Two-thirds of children with IAND were aged ≤4 years; less than half had pre-existing neurological disease or other risk factors for severe influenza. IAE caused death or neurological morbidity in half of cases.

Our study revealed that clinical presentation at admission was fever seen in 120, neurologic manifestations were seizures in 84, altered consciousness in 96, ataxia in 52 and respiratory manifestations were cough in 34 and dyspnea in 67. Complications were acute necrotizing encephalitis (ANE) in 68, hemorrhagic shock in 34 and mild encephalopathy with reversible splenial lesions (MERS) in 26. Mastrolia et al,[16] observed that fifteen children had influenza-associated central nervous system (CNS) manifestations. Eight patients (53.3%) were diagnosed as influenza encephalitis, 7 (46.7%) as influenza encephalopathy. Median age was 27 months. In children under 2 years of age (40% of all cases) altered consciousness was the most frequent neurological manifestation while respiratory symptoms were present at admission in all cases. Younger children also required intensive care support more frequently. Five subjects (33.3%) presented comorbidity. None of the patients had received seasonal influenza vaccination. The median time from onset of respiratory signs to onset of neurological manifestations was 24 hours. Cerebrospinal fluid (CSF) analysis was normal in most patients and polymerase chain reaction for influenza virus RNA on CSF, when performed, was negative in all samples. Neuroradiological investigations, performed in 5 children, reported cortical and subcortical white matter signal alterations. Oseltamivir was administered only in 2 cases. Fourteen patients recovered without sequelae, and only a 2-year-old girl had minimal impairment in fine motor skills at discharge.

CONCLUSION

All children with acute neurological features during influenza season should be assessed for influenza-associated CNS complications. Most common complication was acute necrotizing encephalitis.

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