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ORIGINAL ARTICLE

Neurological Manifestations of Influenza A (H1N1): Clinical Features, Intensive Care Needs, and Outcome

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Abstract

Objectives To describe neurological manifestations in children with Influenza A (H1N1).

Methods This retrospective study was conducted in the Pediatric intensive care unit (PICU) and Pediatric Neurology unit of a tertiary care teaching hospital in North India involving children with PCR confirmed Influenza A (H1N1) with neurological manifestations during 2019 outbreak.

Results Six children (5 females, 1 male) were enrolled. All presented with neurological symptoms (seizures and altered sensorium) accompanied with fever and respiratory symptoms with duration of illness of 2–7 d. The admission Glasgow Coma Scale ranged from 4 to 12. Only 2 cases showed cerebrospinal fluid pleocytosis. Neuroimaging was suggestive of diffuse cerebral edema, acute necrotizing encephalopathy of childhood, and acute disseminated encephalomyelitis. All were treated with Oseltamivir. Four cases had clinical features of raised intracranial pressure (ICP) and were managed in PICU, 3 of them needed mechanical ventilation, 3 needed vasoactive drugs, 3 received 3% saline infusion, 1 underwent invasive ICP monitoring, and 3 (cases 4, 5 and 6) received intravenous methylprednisolone (30 mg/kg) for 5 d. Total duration of hospital stay was 10–30 d. Case 2 expired due to refractory raised ICP. Among survivors, 3 children had residual neurological deficits and the remaining 2 had achieved premorbid condition.

Conclusions Influenza A (H1N1) can present with isolated or predominant neurological manifestations which can contribute to poor outcome. The authors suggest to rule out H1N1 in any child who presents with unexplained neurological manifestations during seasonal outbreaks of H1N1.

Keywords Encephalitis · Demyelination · Influenza · Raised intracranial pressure

Introduction

Influenza A (H1N1) virus usually involves respiratory system and is known for self-limiting flu like illness including fever, cough, rhinorrhea, and sore throat. Multiorgan involvement can occur in patients with influenza, leading to unusual presentations and severe complications causing significant morbidity and mortality [1–3]. Uncommonly, H1N1 also causes a wide plethora of neurological complications including seizure, encephalitis, encephalopathy, raised intracranial pressure (ICP), acute disseminated encephalomyelitis (ADEM), acute necrotizing encephalopathy of childhood (ANEC), Guillain-Barre syndrome, and transverse myelitis. [4–18].

The data about neurological manifestations in Influenza A (H1N1) in children from Indian subcontinent is limited to few case reports only [19, 20]. In the present report, authors present 6 children (previously well) with Influenza A (H1N1) during 2019 outbreak with neurological manifestations in form of seizures, encephalopathy, encephalitis, raised ICP, ANEC and ADEM. The prominent radiological abnormalities are also demonstrated. Whenever any child presents with unexplained neurological manifestations during seasonal outbreak of H1N1, one should upfront start on empirical Oseltamivir after sending the investigations for the same.

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Material and Methods

This retrospective study involves chart review of the children admitted in the Pediatric intensive care unit (PICU) and Pediatric Neurology unit of a tertiary care teaching hospital in North India over a period of 4 mo (January 2019 through April 2019). The authors identified 6 children with laboratory confirmed H1N1 infection with predominant neurological manifestations. The patients were diagnosed by the Centers for Disease Control recommended real time polymerase chain reaction (CDC-RT-PCR) from nasopharyngeal aspirations or swabs. The data was collected from the case records regarding demographic profile, clinical features, neurological signs and symptoms, laboratory investigations, neuroimaging, treatment details, intensive care needs, complications, and outcome. Since this was a retrospective study, patient consent was not obtained. The approval was obtained from the Departmental Review Board.

Results

During the influenza season of 2019 (January–April), 68 Influenza A (H1N1) cases were admitted to the hospital. Out of them, ten (14.7%) cases were admitted to PICU and Pediatric Neurology unit, and 6 (8.8%) had neurological manifestations due to Influenza A (H1N1). Five out of 6 cases were females with an age range of 6 mo to 10 y (median age 25 mo). All the cases were previously healthy. They had an illness duration of 2–7 d. All cases had fever and respiratory symptoms (cough, coryza, respiratory distress), and one had rash over extremities and face. All the cases had seizures and altered sensorium at admission with GCS ranging from 4 to 12. They had generalized tonic-clonic seizures. Clinical signs of raised ICP (tachycardia, bradycardia, hypertension, unequal pupils, hypertonia, brisk deep tendon reflexes, pupillary inequality, or abnormal respiration) were noted in 4 cases. One case had focal deficit in form of left hemiparesis (Table 1).

Chest radiographs were abnormal in 3 cases (bilateral infiltrates in cases 1 and 6; right middle zone consolidation in case 4). Cerebrospinal fluid analysis revealed normal sugar and protein ($n = 5$) and pleocytosis in terms of 9–10 cells/cumm with lymphocytic predominance ($n = 2$) (Table 1).

Patient 1 and 3 had normal contrast enhanced magnetic resonance imaging (CE MRI) brain and contrast enhanced computerized tomography (CECT) brain, respectively. Patient 2 had diffuse cerebral edema on CECT brain. MRI brain was suggestive of ANEC in Patient 4 and 5 (Figs. 1 and 2, respectively) and ADEM in patient 6 (Fig. 3).

Cases 1–4 had respiratory failure at admission to Pediatric emergency, 3 cases had hemodynamic compromization, 1 had acute kidney injury (AKI), and 2 had transaminitis. All cases were treated with Oseltamivir for 5 d. Four cases with features of raised ICP were managed in PICU. Out of these 4 cases, 3 needed mechanical ventilation, and 3 cases with hemodynamic instability required vasoactive drugs, 3 received 3% saline infusion for raised ICP, and one case (case 4) underwent invasive ICP measurement by intraparenchymal ICP catheter (Table 2). Three cases (cases 4, 5, and 6) received intravenous methylprednisolone (30 mg/kg) for 5 d followed by oral prednisolone for 4–6 wk for para-infectious immunological neuroimaging findings.

The clinical presentation of cases 1 and 3 were labelled as encephalopathy and raised ICP; case 2 as encephalitis, cerebral edema, and refractory raised ICP; case 4 as ANEC with raised ICP, case 5 as ANEC, and case 6 as ADEM. Case 2 expired on day 3 of admission in PICU due to diffuse cerebral edema, raised ICP, and brainstem herniation. The total duration of PICU stay was 10–21 d among PICU survivors (10, 14, and 21 d). Total duration of hospital stay was 10–30 d. Among survivors, 2 cases had residual neurological deficits and 3 were in premorbid condition (Table 2).

Discussion

The experience of neurological manifestations in 6 children with Influenza A (H1N1) is being reported from a tertiary care teaching hospital in North India. The clinical presentations in these 6 children were encephalopathy, encephalitis, cerebral edema, raised ICP, ANEC, and ADEM. The authors also described clinical profile, neuroimaging findings, CSF abnormalities, treatment details, intensive care needs, and outcome.

The occurrence of neurological complications is uncommon with seasonal influenza where an estimated incidence of around 1.2 per 100,000 children per year is being observed [14, 21]. The pathogenesis of influenza associated encephalitis and encephalopathy is postulated to be due to direct viral invasion of central nervous system, metabolic encephalopathy coexisting with severe influenza illness, and a dysregulated immune response [22].

The literature on neurological manifestations in children with Influenza A (H1N1) is limited to studies from west and east Asian countries [4–18] with only few case reports from India [19, 20]. The salient features of various studies involving children with neurological manifestations of H1N1 are shown in Table 3. Amin et al. [5] reported 14 children with acute childhood encephalitis and encephalopathy associated with seasonal influenza and noted that 64% had neurological manifestations within 5 d of onset of respiratory symptoms and >50% had neurological sequelae. Kedia et al. [9], in a retrospective study demonstrated that neurological complications were noted in 7.5% (23/307) cases during 2009 Influenza A (H1N1) pandemic, 65% (15/23) needed intensive

Table 1 Demographic profile, clinical features, neurological manifestations, and investigations in children with Influenza A (H1N1) with neurological manifestations

Patients	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	6 mo	10 y	3 y	$4^1/_2$ y	1 y	15 mo
Sex	Female	Female	Female	Female	Female	Male
Premorbid status	Normal	Normal	Normal	Normal	Normal	Normal
Duration of illness (days)	4	2	3	7	7	5
Fever	+	+	+	+	+	+
Cough	+	+	+	+	+	+
Coryza	+	–	–	+	+	–
Respiratory distress	+	+	–	+	–	–
Rash	–	–	–	+	–	–
Seizures	+	+	+	+	+	+
Altered sensorium	+	+	+	+	+	+
Focal features	–	–	–	–	+	–
GCS at admission	7	4	7	4	8	12
Clinically raised ICP	+	+	+	+	–	–
Chest radiograph	Abnormal	Normal	Normal	Abnormal	Normal	Abnormal
CSF						
WBC (per mm^3)	0	ND	0	9 (100%)[1]	10 (100%)[1]	0
Glucose (mg/dl)	129		95	101	47	76
Protein (mg/dl)	30		30	32	21	42

CSF Cerebrospinal fluid, *GCS* Glasgow coma scale, *ICP* Intracranial pressure, *ND* Not done, [1] Lymphocytes

care, 50% (3/6) had elevated CSF proteins but no significant pleocytosis, 83.3% (5/6) had abnormal MRI brain, 13% died, and 22% had short-term disability. Goenka et al. [8] reported 25 cases (21 children and 4 adults) of H1N1 with neurological manifestations, 80% ($n = 20$) needed intensive care, 16% ($n = 4$) died, and 68% ($n = 17$) had poor outcome. Similarly, Khandaker et al. [16] and Wilking et al. [17] also demonstrated that 8.8% - 9.7% children with H1N1 developed neurological manifestations, 1/3rd to 2/3rd cases required ICU admission, and 25% - 50% needed mechanical ventilation. Other studies also reported poor neurological outcome and sequelae [4, 7, 8].

Similar to above studies, the authors of present study also noted that 8.8% children with Influenza A (H1N1) developed neurological manifestations. As per available literature, 10–30% cases with Influenza A (H1N1) need intensive care [6, 15, 16], which is similar to the current study where 14.7% required PICU admission. Out of 6 children with neurological manifestations, 4 (66.7%) required ICU care and 50% required mechanical ventilation. This is at par with literature,

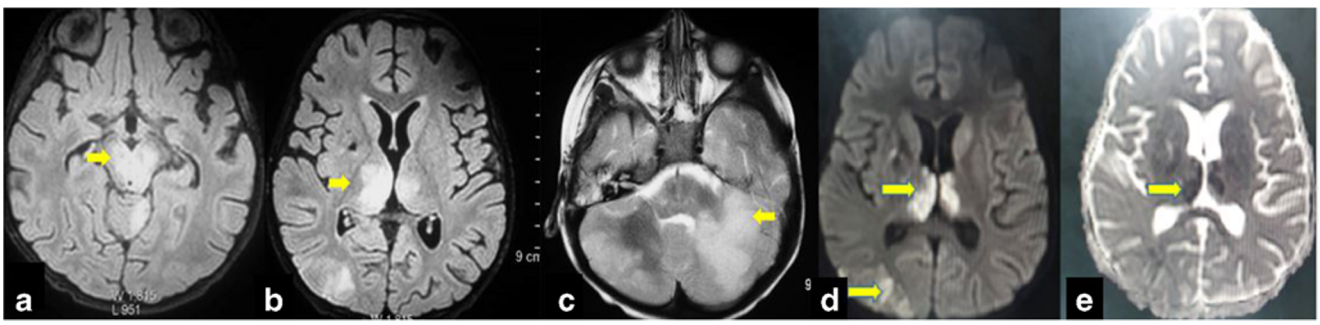

Fig. 1 MRI brain of patient 4. Axial sections at the level of basal ganglia and pons showing T2 (**a** and **c**) FLAIR (**b**) hyperintensities in the midbrain, bilateral basal ganglia, right parietooccipital area, left middle cerebellar peduncle, and patchy hyperintensities in bilateral cerebellar hemisphere. Corresponding diffusion weighted image (**d**) and apparent diffusion coefficient images (**e**) showing intense diffusion restriction in the bilateral basal ganglia and right parietooccipital white matter changes. Susceptibility weighted images showed punctate hemorrhagic changes in the thalamus and right putamen *(not in figure)*. The imaging finding were consistent with diagnosis of acute necrotizing encephalopathy of childhood (ANEC)

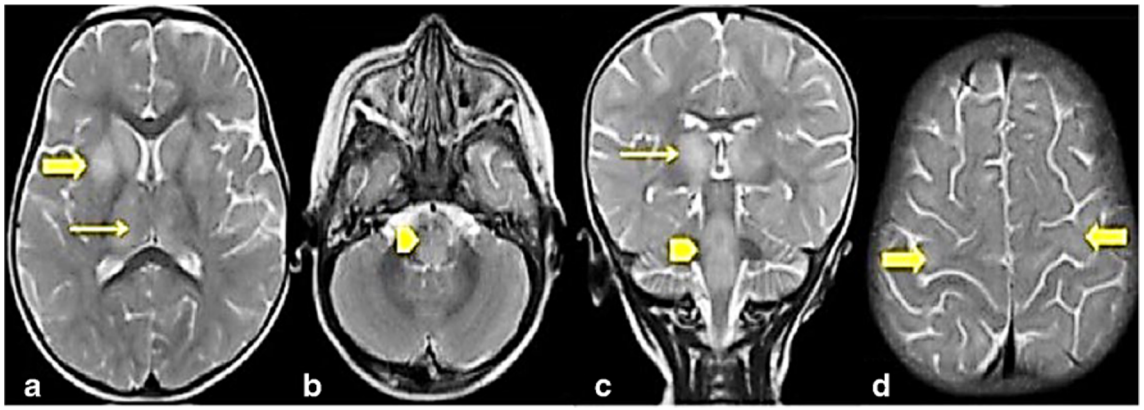

Fig. 2 MRI brain of patient 5. Axial T2 weighted images (**a, b, d**) at the level of the basal ganglia, upper medullar, and high frontal area, respectively showing T2 hyperintensities in bilateral caudate heads, putamen, thalamus, pons and subcortical white matter in high frontal and parietal area. Coronal T2 weighted images (**c**) showing hyperintense signal changes in bilateral thalamus, midbrain, pons and medullary area. Note made of swollen bilateral thalamus. The imaging findings were suggestive of acute necrotizing encephalopathy of childhood (ANEC)

where in presence of neurological manifestations, 30% to 2/3rd needed ICU admission and 25%–50% cases required mechanical ventilation [16, 17]. Patient 4 and 5 had ANEC and survived with significant sequelae. ANEC is special form of encephalopathy with higher mortality and sequelae [12, 13].

The radiological abnormalities noted in Influenza A (H1N1) are bilaterally symmetrical basal ganglia and deep nuclei abnormalities, and widespread white matter abnormalities (typical of ADEM) [12, 13, 23–25]. Kimura et al. divided influenza-related brain changes into five categories based on the MRI brain and CT findings [10]. These include: normal (category 1), diffuse involvement of the cerebral cortex (category 2), diffuse brain edema (category 3), symmetric involvement of the thalamus (category 4), and focal encephalitis (category 5). As noted in the current study, previous studies also noted absence of pleocytosis [12, 13, 23, 24, 26].

Treatment of Influenza A (H1N1)-infected patients with neuraminidase inhibitors (Oseltamivir or Zanamivir) leads to reduction in duration of illness by 0.5 to 1.5 d, reduction in rate of complications, hospitalization, and mortality; and improved outcome [15, 27]. There are no randomized, controlled studies examining the efficacy of antiviral treatment on influenza-related neurologic complications and it is not clear whether the prognosis is better following treatment. With the available literature, it is advisable to start the antiviral therapy in Influenza A (H1N1) patients with neurological symptoms or complications as soon as possible. Thus, patients ($n = 6$) in current study were administered oral Oseltamivir for 5 d.

The outcome associated with neurological complications in patients with Influenza A (H1N1) is highly variable ranging

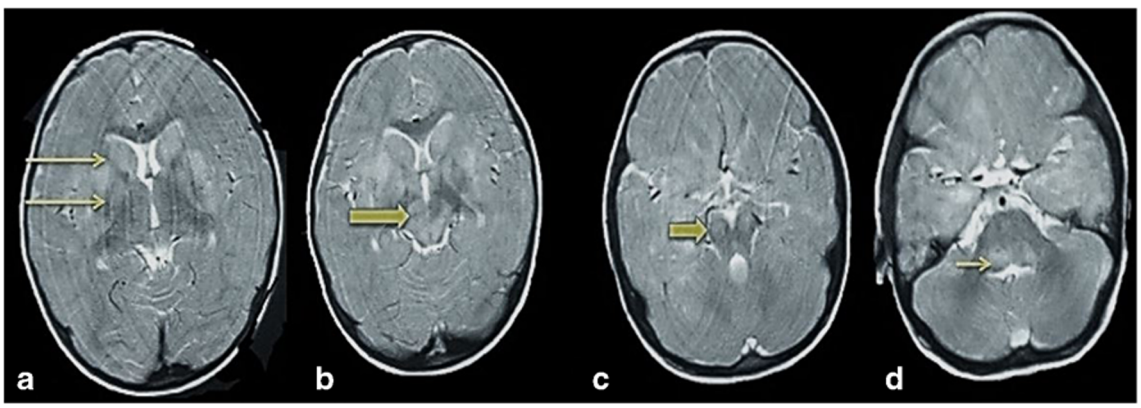

Fig. 3 MRI brain of patient 6. The rostral to caudal axial T2 weighted images showing bilateral symmetrical hyperintensities in bilateral caudate, putamen, medial thalamus, external capsular white matter (**a**), diffuse involvement of the dorsal midbrain (**b**), ventral midbrain including substantia nigra (**c**) and dorsal pons (**d**). The imaging findings were suggestive of acute disseminated encephalomyelitis (ADEM)

Table 2 Complications, treatment, intensive care needs, and outcome of children with Influenza A (H1N1) with neurological complications

Patients	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Respiratory failure	+	+	+	+	–	–
Hemodynamic instability	+	+	–	+	–	–
Acute kidney injury	–	+	–	–	–	–
Transaminitis	+	+	–	–	–	–
Oseltamivir	+	+	+	+	+	+
Mechanical ventilation	+	+	–	+	–	–
Vasoactive support	+	+	–	+	–	–
ICP catheter insertion	–	–	–	+	–	–
3% saline infusion	–	+	+	+	–	–
Steroids	–	–	–	+	+	+
Duration of PICU stay (days)	21	3	10	14	–	–
Duration of hospital stay (days)	30	–	14	18	10	10
Neurological manifestations	Encephalopathy	Encephalitis, cerebral edema, refractory raised ICP	Encephalopathy	Acute necrotizing encephalopathy of childhood, raised ICP	Acute necrotizing encephalopathy of childhood.	Acute disseminated encephalomyelitis
Outcome	Survived	Expired	Survived	Survived	Survived	Survived
Neurological sequelae	Premorbid status	–	Premorbid status	Intermittent dystonia	Left hemiparesis, mutism	Premorbid status
PCPC scale at discharge	1	6	1	4	4	2

ICP Intracranial pressure, *PCPC* Pediatric cerebral performance category scale, *PICU* Pediatric intensive care unit

Table 3 Salient features noted in different studies involving children with H1N1 and neurological manifestations

S.no.	Author [reference]	Number of children of H1N1 with neurological manifestations	Salient findings
1	Amin et al. [5]	14	• 78.6% were < 5 y of age. • 93% cases had respiratory prodrome. • Neuroimaging abnormalities were common in children <2 y. • >50% had neurological sequelae.
2	Kedia et al. [9]	23 out of 307 (7.5%) cases of Pediatric Influenza A (H1N1) cases during pandemic influenza of 2009	• Seizures (62%) and encephalopathy (26%) were most common presentations. • 65% needed PICU admission for a median duration of 4 d. • MRI brain was abnormal in 5 of 6 children. • 13% died and 22% had short-term disability.
3	Goenka et al. [8]	25 cases (21 children and 4 adults)	• Among children, 12 had encephalopathy, 8 had encephalitis, and 1 had meningoencephalitis. • 80% needed intensive care. • 16% died. • 68% had poor neurological outcome.
4	Khandaker et al. [16]	49 out of 506 (9.7%) children with H1N1	• 31% needed ICU admission. • 25% required mechanical ventilation. • 4.1% died.
5	Wilking et al. [17]	32 out of 365 (8.8%) children with H1N1	• Seizure (53.1%), encephalitis (12.5%), meningitis (12.5%), encephalopathy (9.4%), meningismus (9.4%), and focal hemorrhagic brain lesions (6.3%) were common features. • 2/3rd required ICU admission. • 50% required mechanical ventilation. • No mortality.
6	Current study	6	• All had fever, respiratory symptoms, seizures and altered sensorium. • Admission GCS ranged from 4 to 12. • Neuroimaging showed diffuse cerebral edema, ANEC and ADEM. • 4 cases had raised ICP and required PICU admission. • Duration of hospital stay was 10–30 d. • One died and 3 cases had neurological deficits.

ADEM Acute disseminated encephalomyelitis, *ANEC* Acute necrotizing encephalopathy of childhood, *GCS* Glasgow coma scale, *ICP* Intracranial pressure, *ICU* Intensive care unit, *MRI* Magnetic resonance imaging, *PICU* Pediatric intensive care unit

from self-limiting to severe complications. The mortality rate varied between 4 and 30% [16, 22, 28]. In the current study the mortality was 16.6% (1/6) whereas 40% (2/5) of survivors developed sequelae.

Conclusions

H1N1 infection may lead to neurological manifestations associated with poor outcome. During outbreaks season, high index of suspicion should be kept in children presenting with neurological symptoms with or without respiratory involvements and should be empirically started on Oseltamivir after sending the investigations for confirmation. Prompt diagnosis, early initiation of antiviral therapy, and supportive care are mainstay of preventing complications and early recovery.

Authors' Contributions LT: Clinical management of cases, data collection, review of literature, and drafted initial manuscript; LS: Supervised clinical management, reviewed the manuscript, and provided intellectual inputs; SK: Clinical inputs and review of literature; SKA: Planned the study, supervised patient management, and finalized the manuscript; KN: Supervised patient management and critically reviewed manuscript; RS: Supervised patient management and critically reviewed the manuscript; SV: Supervised clinical management of cases; PS: Helped in radiological

diagnosis; KG: Helped in virological diagnosis; RKR: Helped in virological diagnosis and provided intellectual inputs for the manuscript; MJ: Supervised clinical management, reviewed the manuscript and will act as Guarantor for this paper.

Compliance with Ethical Standards

Conflict of Interest None.

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