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ORIGINAL PAPER

Neurological complications of pandemic influenza (H1N1) in children

Dinçer Yıldızdaş · Tanıl Kendirli · Ali Ertuğ Arslanköylü · Özden Özgür Horoz · Faruk İncecik · Erdal İnce · Ergin Çiftçi

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Abstract The aim of this study was to determine the clinical characteristics of children demonstrating neurological complications with pandemic influenza (H1N1). We reviewed the medical and laboratory records of all children who were hospitalized with neurological symptoms and who had proven influenza virus infection by reverse transcriptase–polymerase chain reaction on nasal and throat swabs. Eight children aged between 10 months and 7 years had neurological complications due to pandemic influenza (H1N1) and five of them were female. Four of them were previously healthy; there was chronic renal failure (CRF) in one and neurologic disease in three patients. Seven of them had seizure and altered consciousness. Seven of them were followed in pediatric intensive care units. We performed lumbar puncture in four patients and their cerebrospinal fluid examinations showed pleocytosis in one and no cell in three specimens. Neuroimaging was performed in four patients and three of them had abnormalities. We diagnosed aseptic meningitis in one, acute disseminated encephalomyelitis (ADEM) in one, acute necrotizing encephalopathy (ANE) in one, meningoencephalitis in one, and status epilepticus in four patients. All patients were treated with oseltamivir and antiepileptic drugs. One patient with CRF died; four previously healthy patients recovered fully, and three patients who had neurologic disorder returned to their previous neurological status. In conclusion, during pandemic influenza (H1N1) infection, neurological complications may be seen in addition to the respiratory infection. The type of neurological involvement may be variable such as triggering seizure, aseptic meningitis, encephalitis, ADEM, and ANE. Neurological complications frequently recover fully especially in previously healthy children, but sometimes a severe clinical course occurs.

Keywords Pandemic influenza (H1N1) · Neurological complication · Seizure · Altered consciousness

D. Yıldızdaş · Ö. Ö. Horoz
Department of Pediatric Intensive Care,
Çukurova University School of Medicine,
Adana, Turkey

T. Kendirli (✉)
Departments of Pediatric Intensive Care,
Ankara University School of Medicine,
Ankara, Turkey
e-mail: tanilkendirli@hotmail.com

A. E. Arslanköylü
Department of Pediatric Intensive Care,
Mersin University School of Medicine,
Mersin, Turkey

F. İncecik
Department of Pediatric Neurology,
Çukurova University School of Medicine,
Adana, Turkey

E. İnce · E. Çiftçi
Departments of Pediatric Infectious Disease,
Ankara University School of Medicine,
Ankara, Turkey

Introduction

Pandemic influenza (H1N1) started in the Mexican town of La Gloria, Veracruz, in mid-February 2009 [14]. The World Health Organization (WHO) declared a pandemic of a novel virus as pandemic influenza (H1N1), on June 11, 2009 [4]. Finally, in March 2010, WHO reported that cases with pandemic influenza (H1N1) had been seen in almost all countries with more than 17,700 deaths among laboratory-confirmed cases [5].

Between November 12 and December 30, 2009, The Ministry of Health of Turkey reported periodical updates about pandemic influenza (H1N1) outbreak in Turkey. During this period, approximately 6.5 million people were infected and 13,111 patients were hospitalized, 2,721 patients were admitted to intensive care units, 1,161 patients were mechanically ventilated, and 627 people died due to pandemic influenza (H1N1) [26]. But, there was no acknowledgement about neurological complications associated with pandemic influenza (H1N1) infections in Turkey.

Extrapulmonary symptoms such as gastrointestinal and neurological findings were seen during pandemic influenza (H1N1) outbreak. Neurological complications including seizure, Reye's syndrome, aseptic meningitis, encephalitis, encephalopathy, acute disseminated encephalopathy (ADEM), Gullian-Barré syndrome, transverse myelitis, acute necrotizing encephalopathy (ANE), and other neurological disorders have been described previously in association with respiratory tract infection with seasonal influenza A and B viruses [12, 15], but there are only few reports about neurological involvement due to pandemic influenza (H1N1) infection in children [2, 3, 11, 13, 19, 21]. Here, we report neurological complications in eight children with pandemic influenza (H1N1) infection.

Materials and methods

Children included in this study were between 1 month and 18 years old, with neurological involvement of pandemic influenza (H1N1). Patients were followed up at three different children's hospitals in Turkey. Clinical and laboratory data were collected from patients' medical records.

Together a study form was prepared by all centers. Each form was filled for each patient, with neurological involvement, who was admitted to pediatric intensive care and pediatric infectious disease services. This form consisted of patients' demographic data, underlying illness, presenting symptoms, clinical and laboratory findings, seizure type, neuroimaging, oseltamivir and antiepileptic drugs usage, microbiological investigations, Pediatric Index of Mortality II (PIM II), Pediatric Logistic Organ Dysfunction Score (PELOD), respiratory supports, nosocomial infections, and outcome [9, 24]. In laboratory tests, we performed white blood cell count (WBC), hemoglobin (Hb), platelet (Plt) count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), blood glucose, blood urea nitrogen (BUN), sodium, potassium, calcium, magnesium, aspartate, and alanine transaminase in all patients.

The diagnosis of pandemic influenza (H1N1) infection was confirmed by testing nasal aspirates or combined nasal and throat swabs with the use of real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay at national laboratories. This test assessed both pandemic influenza (H1N1) and seasonal influenza at the same sample, separately. Other respiratory tract viruses including adenovirus, rhinovirus, respiratory syncytial virus, and parainfluenza virus were not tested routinely.

A child with acute neurological complications associated with novel influenza (H1N1) infection was defined as having laboratory-confirmed pandemic influenza (H1N1) virus infection of the respiratory tract associated with seizures, encephalopathy, or encephalitis within 5 days of influenza-like illness symptom onset, without evidence of an alternative etiology. Encephalopathy was defined as altered mental status lasting ≥24 h. Encephalitis was defined as encephalopathy plus two or more of the following: fever ≥38°C, focal neurological signs, cerebrospinal fluid (CSF) pleocytosis, electroencephalogram (EEG) indicative encephalitis, or abnormal neuroimaging indicative of infection or inflammation [15, 16]. This study was conducted as a retrospective multicenter study. The individual institutional review boards reviewed and approved this study.

Results

Between October 15, 2009 and January 15, 2010, a total of 73 hospitalized children were diagnosed with proven pandemic influenza (H1N1) infection by RT-PCR in three centers. Twenty-one (28.7%) of them were followed at pediatric intensive care unit (PICU) and eight (10.9%) patients had neurological involvement together with upper or lower respiratory infections. All of them were unvaccinated for pandemic influenza (H1N1) and seasonal influenza. Clinical characteristics and laboratory data of the patients are given in Table 1; investigations and outcome of patients are shown in Table 2. We presented abnormal laboratory values, but we did not give normal results, and instead, we remarked them as normal in text. Neurological complications included aseptic meningitis, meningoencephalitis, ADEM, ANE, new-onset seizures in previously healthy children, or increased seizure frequency in patients with epilepsy that could not be explained on the basis of metabolic abnormalities.

Patients

Patient 1

A previously healthy, 6-year-old girl had fever (39°C), headache, and vomiting for which she was brought to

Table 1 Clinical characteristics and laboratory data of patients with neurological complications due to pandemic influenza (H1N1) infection

Patient	Age / gender	Co-morbidity	Presentation	Examination on admission	Seizure type	CSF analysis
1	6 y, F	Healthy	Fever, headache, vomiting	BT 39.2°C, oropharynx hyperemic, nuchal rigidity, GCS 15	N	Opening pressure high, opalescent, WBC 1310/mm^3, 2% PMNL, 98% lymphocyte, protein 59 mg/dL, glucose 49 mg/dL
2	6 y, M	Healthy	Fever, altered consciousness, seizure, cough	BT 38.4°C, GCS 8, PIM II 18.8%, PELOD score 11	GTC, SE	Appearance clear, WBC 0/mm^3, protein 30.5 mg/dL, glucose 101 mg/dL
3	10 m, F	Healthy	Respiratory distress, cough, seizure, altered consciousness	Respiratory distress, GCS 10, PIM II 2.9%	GTC	ND
4	3 y, M	Healthy	Fever, altered consciousness, seizure	BT 38.1°C, GCS 9, PIM II 2.4%, PELOD 1	GTC, SE	ND
5	4 y, F	CRF	Fever, fatigue, myalgia, seizure, altered consciousness	BT 39.5°C, GCS 3, PIM II 98.4%, PELOD 53	GTC, SE	ND
6	3 y, M	West syndrome	Fever, cough, seizure, altered consciousness	BT 38.7°C, GCS 9, pharynx hyperemic	GTC, SE	Opening pressure 21 cmH2O, clear, WBC 0/mm^3, protein 40 mg/dL, glucose 57 mg/dL
7	6 y, F	CP, epilepsy	Fever, cough, increased seizure frequency, altered consciousness	BT 38.4°C, GCS 10, rales bilaterally, PIM II 0.7%, PELOD 0	GTC, SE	ND
8	7 y, F	CP, epilepsy	Fever, increased seizure frequency, altered consciousness	BT 38.2°C, GCS 10, PIM II 3.4%, PELOD 0	GTC, SE	Opening pressure 12 cmH2O, clear, WBC 0/mm^3, protein 44 mg/dL, glucose 80 mg/dL

M male, *F* female, *N*: No, *CSF* cerebrospinal fluid, *BT* body temperature (axillary), *WBC* white blood cell, *GCS* Glasgow Coma Scale, *PIM II* Pediatric Risk of Mortality II, *PELOD* Pediatric Logistic Organ Dysfunction, *CRF* crenal failure, *ND* Not done, GTC Generalized tonic–clonic, SE, Status epilepticus, *CP* Cerebral palsy, *y* year, *m* month

pediatric emergency care unit. There was fever for 1 day, headache for 12 h, and vomiting six times in the last 24 h. Also, there were infected children by pandemic influenza (H1N1) in her school. On physical examination, physical development was within normal limits; she was exhausted, and her body temperature was 39.2°C; her oropharynx was hyperemic. On neurological examination, she was conscious; Glasgow Coma Scale (GCS) result was 15; meningeal irritation findings were positive.

In her laboratory data; Hb was 12.8 g/dL, WBC was 14,800/mm^3, Plt count was 309,000/mm^3, ESR was 20 mm/h, and CRP was 6.1 mg /dL (normal range, 0–0.8 mg/dL). Patient's biochemical and urine analysis were normal. We performed lumbar punction (LP), and there was

Table 2 Investigation and outcome of cases

Patients	Neuroimaging	EEG	Diagnosis	Treatments	Outcome
1	ND	ND	Aseptic meningitis	Oseltamivir	Recovery
2	Initial CT normal, MRI showed increased T2 hyperintense signal at diffuse cortical region and perirolandic areas	Sharp waves on right temporo-occipital region	ADEM	Oseltamivir, IVIG, acyclovir, midazolam, phenytoin	Recovery
3	CT showed diffuse brain edema, lost of gray and white region border, decreased sulcia	Spikes, slow waves on mid and posterior regions of left hemisphere	Meningoencephalitis	Oseltamivir, midazolam, phenytion, phenobarbital, hypertonic saline	Recovery
4	CT and MRI normal	Normal	Febrile SE	Oseltamivir, diazepam, phenytoin, phenobarbital	Recovery
5	MRI showed hyperintense lesion in the both thalami, cerebellum, and pons	ND	ANE	Oseltamivir, MV, dopamine, dobutamine, epinephrine, meropenem	Died
6	ND	Severe irregular rhythm	SE	Oseltamivir, diazepam, midazolam, phenobarbital	Recovery
7	ND	Normal	SE	Oseltamivir, diazepam, phenytoin	Recovery
8	ND	Ground activity irregularity and epileptic activity	SE	Oseltamivir, midazolam, phenytoin, phenobarbital	Recovery

ND not done, *EEG* electroencephalogram, *CT* computed tomography, *MRI* magnetic resonance imaging, *MV* mechanical ventilation, SE Status epilepticus

high opening CSF pressure and the appearance was opalescent; and 1.310/mm^3 of WBC (98% lymphocyte and 2% PMNL), biochemical parameters; protein was 59 mg/dL, and glucose was 49 mg/dL (simultaneous blood glucose was 99 mg/dL).

No microorganisms grew in blood, throat, urine, and CSF cultures. Pandemic influenza (H1N1) RT-PCR was positive on nasal and throat swabs. The diagnosis of aseptic meningitis due to pandemic influenza (H1N1) was established. Oseltamivir was initiated on third day of her hospitalization. The patient's fever decreased within 24 hours. Her clinical findings showed that she recovered fully. She was discharged at fifth day of admission, and oseltamivir therapy was completed to 5 days.

Patient 2

A previously healthy 6-year-old boy who was brought to pediatric emergency care because of fever, cough, seizure, and altered mental status. There was fever for 4 days, cough for 2 days and neurological symptoms started at the same day. On his physical examination, axillary body temperature was 38.4°C, oropharynx was hyperemic, he was unconscious, he could localize painful stimuli, GCS was 8, pupil reaction and fundus findings were bilaterally normal. There was no nuchal rigidity. Kernig and Brudzinski's signs were negative. He was admitted to PICU. Patient's PIM II and PELOD scores were 18.8% and 11%, respectively.

At his laboratory investigations, Hb was 10.5 g/dL, WBC was 10.000/mm^3, Plt count was 153,000/mm^3, CRP was 20.1 mg/dL and also biochemical, urine tests, and arterial blood gases were normal. Chest X-ray was normal.

Initial brain computed tomography (CT) was normal, then magnetic resonance (MRI) was performed for his continuous unconsciousness. In MRI, there was increased T2 hyperintense signal at diffuse cortical region and perirolandic areas. Also there were increased hyperintense areas at thalami (Fig. 1a, b). These findings of brain MRI were diagnostic for ADEM. On EEG, there were sharp waves on right temporo-occipital region. We performed LP and opening pressure was normal, and there was no cell on microscopy. CSF protein was 30.5 mg/dL and glucose was 101 mg/dL (simultaneous blood glucose was 142 mg/dL).

Pandemic influenza (H1N1) RT-PCR was positive on patient's nasal and throat swabs. Herpes virus and enteroviruses PCR were negative in CSF sample. Also, there were no bacteria, virus and parasitic infection on CSF and blood studies. There were no any symptoms for enterovirus, hepatitis A, measles, mumps, rubella, Epstein-Barr virus and bacterial infection. We made the diagnosis of ADEM associated with this novel pandemic virus. We started the patient on oseltamivir for pandemic influenza A infection, intravenous immunoglobulin (400 mg/kg/day) for ADEM, and acyclovir for possible herpes simplex virus (HSV) encephalitis. We started midazolam and phenytoin for recurrent generalized tonic–clonic seizures.

His clinical findings improved and became conscious on the 2nd day of treatment and he healed fully by the 4th day of PICU admission. There was no bacterial growth on culture and HSV RT-PCR was negative in patient's CSF specimens. He was discharged from PICU to pediatric infection service on the 5th day of admission, and discharged to home 2 weeks later as fully recovered.

Patient 3

A previously healthy 10-month-old girl was transferred to PICU from a state hospital for recurrent seizures, mental status alteration, cough and respiratory distress. Pandemic influenza (H1N1) virus RT-PCR had been positive on nasal and throat swabs, also seasonal influenza had been negative

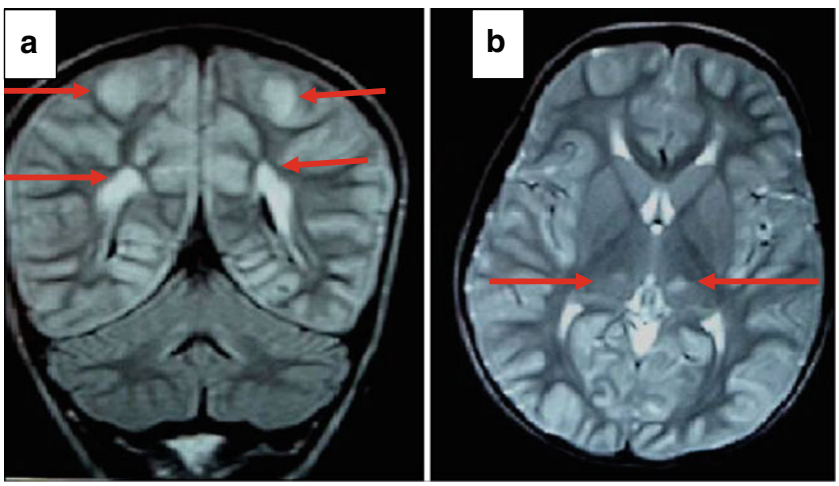

Fig. 1 **a**, **b** Bilateral symmetric hyperintense lesions in the frontoparietal area and periventricular white matter (**a**), thalami (**b**), on T2-wieghted cranial MR images (*arrowed*). These findings were suitable for acute disseminated encephalomyelitis (ADEM)

at same samples and enterovirus had been negative at stool sample. Her GCS was 10 and generalized tonic–clonic seizures were seen 4 times and time to time as blinking. Patient's PIM II score at 24 h was %2,9.

Laboratory data revealed that Hb was 9.2 g/dL, WBC was 5,100/mm^3; Plt count was 13,3000/mm^3, CRP was 13.9 mg/dL, biochemical, blood gases, and urine tests were normal. On cranial CT, diffuse brain edema was obtained. On her EEG; there were spikes, slow waves on mid and posterior regions of left hemisphere. We could not perform LP because of the risk of the herniation since there was brain edema and intracranial pressure, increasing signs on cranial CT. We diagnosed to meningoencephalitis with these findings. In this patient, we could determine only pandemic influenza (H1N1) and accepted that her neurologic course due to pandemic influenza (H1N1).

She was treated with oral oseltamivir (20 days) for pandemic influenza (H1N1) meningoencephalitis; midazolam, phenytoin, and phenobarbital for seizures; and hypertonic saline for brain edema. Her consciousness returned on the fifth day, and she recovered on the seventh day of PICU admission. She was discharged without any neurological sequelae on the 11th day of PICU admission.

Patient 4

A previously healthy 3-year-old boy was brought to pediatric emergency care for fever, acute alteration of consciousness, and seizure. The patient had fever for 1 day, and his fever had increased to 38.9°C. He had one seizure in the last hour at home. He also had generalized tonic–clonic seizure when he was brought to pediatric emergency care. On physical examination, he was unconscious, and GCS was 9. We could not control his status epilepticus with diazepam and phenytoin. Thereafter, he was transferred to PICU. His PIM II score was 2.4%, and his PELOD score, 1.

The patient's complete blood count and biochemical tests were normal. We could not perform LP because of his severe clinical condition, but his cranial CT and MRI were normal. Pandemic influenza (H1N1) was positive on his nasal and throat swabs. We accepted his status as a complicated febrile seizure associated with pandemic influenza (H1N1), and we started him on oseltamivir for severe influenza infection; diazepam, phenytoin, and phenobarbital for complicated febrile seizure; acyclovir for possible encephalitis; ceftriaxone and vancomycin for possible meningitis. We controlled his status epilepticus on the second day; his fever decreased to normal range on third day, and he regained consciousness on third day. He was finally discharged from the PICU on eighth day of admission fully recovered.

Patient 5

A 4-year-old girl with chronic renal failure (CRF) due to vesicoureteral reflux was brought our pediatric emergency care for fever, fatigue, and myalgia complaints. Her symptoms had started 3 days ago. She was admitted to pediatric nephrology service as possible pandemic influenza (H1N1) virus infection with a history of close contact with infected people. On physical examination, her body weight was 11 kg (<3%), body temperature was 39.5°C, blood pressure was 105/65 mmHg, and pharynx was hyperemic; she was conscious and her respiratory and cardiovascular systems were normal. Her whole blood count, blood gases, liver functions, and electrolytes were within normal ranges. We started oseltamivir for possible novel pandemic influenza (H1N1) infection.

At the second day of admission, she had generalized tonic–clonic seizures for three times, and acute mental status changes; then, respiratory arrest developed, and she was intubated. Her pupils were fixed dilated, and her blood pressure 68/32 mmHg when she was transferred to PICU. Her GCS was 3, and PIM II score was 98.4%.

Laboratory data revealed that Hb was 5.3 g/dL; WBC, 4,200/mm^3; Plt count, 60,000/mm^3; CRP, 0.4 mg/dL; BUN, 96 mg/dL; creatinine, 4.5 mg/dL; aspartate aminotransferase, 20,610 IU/L; and alanine aminotransferase, 9,220 IU/L while blood glucose and other biochemical values were normal. Blood gases were pH 7.01, pO_2 79 mmHg, pCO_2 72 mmHg, and HCO_3 14.9. Her PELOD score was 53. Pandemic influenza A (H1N1) 2009 was positive on her nasal and throat swabs.

The intubated patient was mechanically ventilated by conventional mechanical ventilation. She had decompensated shock findings, and we started dopamine, dobutamine, and epinephrine. We also started meropenem in addition to oseltamivir.

However, we could not perform LP because of her circulatory status; we took cranial MRI, and found that there were hyperintense lesions in the both thalami, the cerebellum, and the pons on T2 weighted imaging. These findings were suitable to ANE (Fig. 2a, b).

Brain death developed on second day of PICU admission, and cardiac arrest developed in the same day. We accepted brain herniation/death due to ANE owing to pandemic influenza (H1N1).

Patient 6

A 3-year-old boy with West syndrome and possible mitochondrial myopathy without medication was followed up. He was brought our pediatric emergency care for fever, cough, seizures, and acute mental alteration. At the pediatric emergency care, he had generalized tonic–clonic

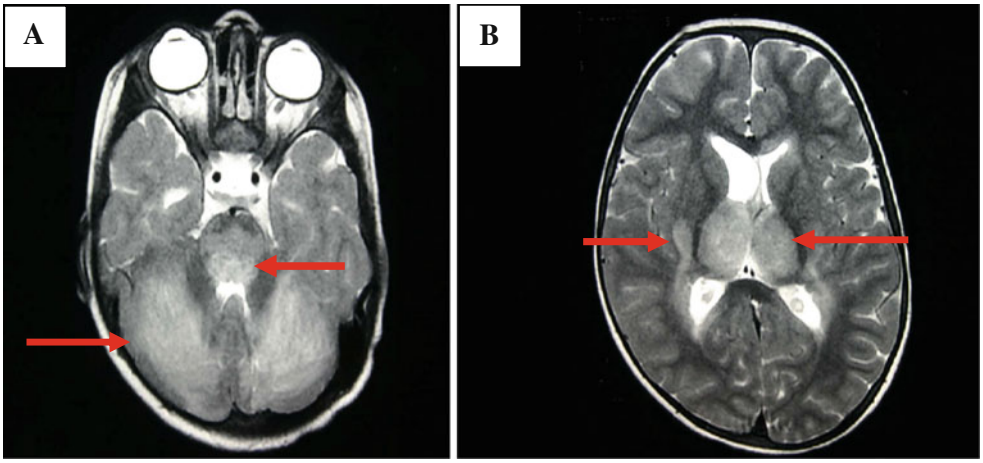

Fig. 2 **a, b** Axial T2-weighted MRI brain scan in patient showing hyperintense lesions in the both cerebellum and pons (**a**), thalami (**b**) (*arrowed*)

seizures for four times in 2 h, mental alteration in 4 h, fever in 4 days, and cough in 2 days, concomitantly. He was admitted to PICU for status epilepticus and mental alteration. On physical examination, he was unconscious with normal bilateral pupillary response and could localize to pain stimulus, and his GCS was 9. Body temperature was 38.7°C, and other vital signs were normal. His pharynx was hyperemic, and other systemic examinations were normal.

Patient's whole blood count and biochemical tests were normal. CSF examination showed opening pressure of 21 cmH_2O, protein, 40 mg/dL, and glucose, 57 mg/dL (simultaneous blood glucose was 90 mg/dL), and there were no cells on microscopic examination. On EEG, there was severe irregular rhythm on ground. Pandemic influenza (H1N1) was positive on nasal and throat swabs.

We accepted him as a case of pandemic influenza-associated status epilepticus, and started him on oseltamivir for influenza infection, and diazepam, midazolam, and phenobarbital for status epilepticus. We succeeded in controlling his severe seizures in the first hours, and his fever decreased to normal range within 2 days, and he regained consciousness at second day of admission. He was discharged on the fifth day of PICU admission.

Patient 7

A 6-year-old girl was brought our pediatric emergency care for fever, cough, and seizure. She had been followed up for epilepsy and cerebral palsy. She was taking levatiracetam for epilepsy. She had fever in 3 days, cough in 2 days, and seizures in last hour. At first, her seizure was focal but then, it changed to generalized tonic–clonic seizure for nearly 10 min. On physical examination, general appearance was moderate, body temperature was 38.4°C, GCS was 10, consciousness altered, and bilateral pupil response to light was normal. There were pharynx hyperemia and rales bilaterally. Her PIM II and PELOD scores were 0.7% and 0, respectively. We admitted her to PICU for status epilepticus.

The patient's whole blood count, acute phase reactants, biochemical, and urine test were normal. We did not need LP, cranial CT, and MRI because she regained consciousness after status epilepticus. Pandemic influenza (H1N1) was positive on her nasal and throat swabs. We accepted her as pandemic influenza (H1N1) associated febrile status epilepticus. We started oseltamivir for influenza infection, and diazepam and phenytoin for febrile seizure. We controlled her seizures in first hours; her body temperature decreased to normal range on fourth day, and she discharged from PICU at sixth day as fully recovered.

Patient 8

A 7-year-old girl who was followed up for cerebral palsy and epilepsy was brought to our pediatric emergency service for increased seizure frequency and fever. Her fever began 3 days ago, and her seizures had increased in last 24 h. She has been treated by lamotrigine and vigabathrine for epilepsy. She was accepted to PICU for status epilepticus and mental alteration. On physical examination, her general appearance was not good, body temperature was 38.2°C, pharynx was hyperemic, and respiratory, cardiovascular, and abdominal examinations were normal. Her GCS was 10, PIM II score was 3.4%, and PELOD score was 0.

Her whole blood count and biochemical tests were normal. We performed LP, and opening pressure was 12 cmH_2O; there was no cell on microscopic examination, and protein was 44 mg/dL, while glucose was 80 mg/dL (simultaneous blood glucose was 110 mg/dL). We did not need brain CT and MRI images. On her EEG, widespread ground activity irregularity and right temporoparietal epileptic activities were seen. Pandemic influenza (H1N1) was positive on nasal and throat swabs. We diagnosed

status epilepticus associated pandemic influenza (H1N1). We started oseltamivir for novel influenza infection, midazolam, phenytoin, and phenobarbital in addition to lamotrigine and vigabatrin for seizures. Her fever decreased on fourth day, and seizures returned in the previous form. Her clinical situation was recovered on sixth day and discharged at ninth day of PICU admission as previous form of neurological condition.

Discussion

Infection with the pandemic influenza (H1N1) virus causes a broad spectrum of clinical courses, ranging from afebrile upper respiratory illness to fulminant viral pneumonia. The chief clinical status leading to hospitalization and intensive care unit are diffuse pneumonia, acute respiratory distress syndrome and sometimes, shock and multiple organ dysfunction syndrome. Neurological involvement is low, but this is important cause for hospital admissions [5, 10, 21]. In our study, we followed 73 hospitalized children during pandemic influenza (H1N1) outbreak in three children's hospitals, and we presented eight (10.9%) of them with neurological complications.

Influenza is a major cause of acute respiratory tract illness each winter. Additionally, influenza virus infection has been associated with variety of neurologic complications. There are some reported large series about influenza-associated neurological complications [1, 16–18]. Newland et al. [17] reported 842 hospitalized children with influenza A infection, and 72 (0.85%) of them had influenza A-related neurologic complications between 2000 and 2004 from the USA. Seizures were seen in 56, encephalopathy in eight, post-infectious encephalopathy in two, stroke caused by hypotension in four, and aseptic meningitis in remaining two patients. In children with only seizure, there is fever in 64%, seizure disorder in 45% of all patients, and their CSF and neuroimaging findings are normal. All patients had survived and neurologic sequelae developed in two patients. Amin et al. [1] reported 14 children with influenza A- (n=13) and B (n=1)-related encephalitis and encephalopathy from January 1994 to December 2004 from Canada. They reported seizures in 12, EEG abnormality in 12, neuroimaging abnormality in nine patients; all of them had survived and neurologic sequelae developed in eight patients. Nagao et al. [16] reported 442 children influenza A- or B-associated encephalopathy between 1998 and 2002 from Japan. Ninety-seven (21.9%) of them died. In our study, we did not determine seasonal influenza and its related neurologic complication in hospitalized patients.

To date, 20 cases with pandemic influenza (H1N1)-related neurologic complications were reported [6–8, 22, 23, 27]. Our cases' clinical, laboratory characteristics, and reported outcomes are given Table 3. Eighteen of them are children, and their ages range from 3 months to 17 years; also, two of them are adults. There are CSF abnormalities in four, neuroimaging abnormalities in eight children, and in two adults. Their diagnoses are encephalitis in five, ADEM in one, encephalopathy in seven, seizure in three, neuropsychiatric syndrome in one, and ANE in three patients. At outcome, death in three, neurologic sequelae in five patients, and 12 of them fully recovered. Brock E [3] reported four children with neurological involvement of pandemic influenza (H1N1). Their ages were 7, 10, 11, and 17 years old. Pandemic influenza (H1N1) was detected on their nasopharyngeal specimens but not on CSF specimens. They had diagnosed them with febrile seizure in one, febrile seizure, and encephalopathy in one, encephalopathy in two patients. Their CSF examination showed 2 and 4/mm^3 of WBC in two patients; glucose levels were normal in range in all patients, increased protein level was (50 mg/dL) in one of four patients. Also, they reported that CT was normal in four and MR was normal three in patients. Only one patient had minimal and nonspecific abnormality in cranial MR. Three of them had abnormality on EEG. Four patients had been given oseltamivir and rimantadine in 3 patients. All children had been recovered and had no neurological sequelae at discharge. Baltagi et al. [2] reported four children with neurological complication due to pandemic influenza (H1N1). In their report, one patient had seizure and three patients had altered mental status. There was no clearly CSF findings, and two of them had neurological sequelae. In our report, one patient died due to ANE due to pandemic influenza (H1N1); also, there were no additional neurological sequelae in others.

We diagnosed aseptic meningitis in one, ADEM in one, ANE in one, meningoencephalitis in one, seizure in four patients owing to pandemic influenza (H1N1) infection. Seven of them were followed in PICU. We could perform LP in four; we could not perform in one because of brain edema. In CSF investigation; patient 1 had pleocytosis. There were neuroimaging in four of them and three of four had abnormalities in cranial CT or MRI. We investigated EEG in six of them and four of six had abnormalities. As outcome, four previously healthy patients fully improved, three patients with neurological disorders returned to their former neurologic status, and one patient who had CRF died due to ANE. Our report demonstrated that pandemic influenza (H1N1) virus infection may have different neurological courses.

In our patients, patients 6, 7, and 8 had neurologic disease before admission to hospital for pandemic influenza (H1N1) infection. Their diagnoses were West syndrome and possible mitochondrial myopathy (patient 6), cerebral palsy and epilepsy (Patient 7 and 8). But, there was

Table 3 Literature review to date about neurologic complications of pandemic influenza (H1N1)

Reports (reference number)	Patient number	Age Range	Presentation	CSF abnormality	Neuroimaging abnormality	Diagnosis	Outcome
CDC [3]	4	7–17 y	Fever, seizure, altered consciousness ,	2 patients	1 patient	Encephalopathy (2), seizure (1) and seizure and encephalopathy (1)	Fully recovered in all
Baltagi SA [2]	4	2–10 y	Fever, seizure, altered consciousness , coma	1 patient	2 patients	Altered mental status (3) and seizure (1)	Neurologic sequele in 2, fully recovered in 2
Lyon JB [11]	1	12 y	Fever, diarrhea, altered consciousness ,	ND	Yes	ANE	Died
Webster RI [27]	2	5 y	Fever, cough, altered consciousness , quadriplegia	1 patient's normal, ND in other	2 patients	Encephalitis	Recovered
Rellosa N [20]	3	23 m–9 y	Fever, confusion, seizure, coma	2 patients had pleocytosis, and other was normal	2 had MR abnormalities and other normal	ADEM (1), fever and SE (1), encephalopathy (1)	Fully recovered in all
Ormitti F [10)	1	3 y	Fever, seizure, cough, diarrhea	6 WBC/mm^3, increased protein (232 mg/dL), numerous red cells	Yes	ANE	Neurologic sequele
Sánchez-Torrent L [22]	1	3 m	Fever, GTC seizure	1160 red blood cell/mm^3, 30 WBC/mm^3	CT Normal	Encephalitis	Recovered
Martin A [13]	1	7 y	Fever, altered consciousness	ND	Yes	ANE	Died
German-Diaz M [7]	1	13 y	Confusion, slow speech, vomiting	Normal	Normal	Neuropsychiatric syndrome	Recovered
Our patients	8	10 m-7 y	Fever, altered conciousness, seizure, coma	Pleocytosis in 1	3 had abnormality	Aseptic meningitis (1), ADEM (1), ANE (1), encephalitis (1), seizure (4)	One Died, 7 recovered
Fugate JE [6]	1	40 y	Fever, comatose status leukoencephalitis	ND Neurologic sequelae	Yes	Hemorrhagic	
Kitcharoen S [8]	1	34 y	Fever, quadriparesthesia, areflexia	Normal	Yes	Encephalitis	Neurologic sequelae

CDC Center for Disease Control, *y* year, *m* month, *CSF* cerebrospinal fluid, *ND*: not done, *ADEM* acute disseminated encephalomyelitis, *ANE* acute necrotizing encephalopathy, *WBC* White blood cell, *CT* computed tomography, *MRI* magnetic resonance imaging, *GTC* generalized tonic–clonic

increased seizure frequency, status epilepticus, and altered consciousness in patients 6, 7 and 8 during pandemic influenza (H1N1) infection. Also, all of them needed PICU admission. Their seizures stopped and consciousness was regained after oseltamivir treatment and recovered pandemic influenza (H1N1) infection. Maricich et al. [12] reported eight children with influenza A infection, and two of them had neurologic disease. One patient had returned basal neurologic state and others had severe neurologic sequelae after influenza A-associated neurologic complication. Newland et al. [17] reported hospitalized children with influenza A infection and 72 (0.85%) of them had influenza A-related neurologic complications. There had seen seizure in 56 children. There was seizure disorder in 45% of children with neurologic complication. The obvious evaluation is difficult when pandemic influenza (H1N1)-associated neurological manifestations developed in a child who has neurologic disorder. For these reasons, we commented they had neurologic disease but pandemic influenza (H1N1) got more serious their neurologic state. After infection controlling, their clinical course returned to their previous neurologic condition.

In our study, patient 5 was diagnosed with ANE. It is an unusual complication of influenza A virus infection that has been in the literature mainly in Japanese children younger than 5 years. In radiologic images, it is typically characterized by multifocal symmetric lesions involving the thalami, brain stem, cerebellum, and white matter. Clinical symptoms often resemble those of influenza encephalopathy and include sudden onset of high fever, severe convulsions, and dramatic neurological deficits rapidly progressing to coma. There is an absence of CSF pleocytosis and metabolic abnormality. Mortality of those with ANE has been reported to reach approximately 30% [11, 17]. There is a reported three children with ANE-associated pandemic influenza (H1N1) [11, 13, 19]. Lyon et al. [11] reported a previously healthy 12-year-old girl who died from ANE-associated pandemic influenza (H1N1) virus infection. Ormitti et al. [19] reported a previously healthy 3-year-old girl who survived with neurological deficit. The other patient is a 7-year-old girl reported by Martin A [13]. She died due to ANE and brain death, like our patient. Patient 5 had CRF, and we admitted her to the hospital for severe flu-like symptoms, but seizures, acute mental alteration, then respiratory arrest developed at second day of admission. On her cranial MR, there were hyperintense lesions in the both thalami, the cerebellum, and the pons (Fig. 2). These findings were suitable for ANE. She died due to ANE and brain death.

The effect of antiviral therapy on critically ill patients with influenza (H1N1 or seasonal) is an area for future larger studies. In the meantime, practitioners are advised to have a high index of suspicion and consider presumptive treatment for all critically ill patients, regardless of duration of symptoms until definitive diagnostic testing available. In our experience, we started oseltamivir in all those admitted to PICU and other services for possible and certain pandemic influenza (H1N1) infection as pneumonia, acute lung injury, acute respiratory distress syndrome and neurological complications [25]. We used oral oseltamivir in all patients with neurological complication due to novel influenza (H1N1) virus. The oseltamivir usage time was 5 days in six patients, 20 days in one patient for his prolonged symptoms, and 2 days in one patient because of her death. There was no adverse effect in patients.

In conclusion, pandemic influenza (H1N1) virus caused a severe outbreak in Turkey between the second half of October and end of December, 2009, similar worldwide. For children who have flu, flu-like symptoms accompanied by unexplained seizures and mental status change, clinicians should consider acute seasonal influenza or pandemic influenza (H1N1) infection in differential diagnosis. The type of neurological involvement may be variable such as triggering seizure, aseptic meningitis, encephalitis, ADEM, and ANE. Neurological complications frequently recover fully in especially previously healthy children, but sometimes severe clinical course and mortality could be seen under co-morbid disease.

Conflicts of Interest The authors declare that they have no conflicts of interest. This study did not receive any financial support.

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