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ABSTRACT. *Objectives.* **Our objectives were to (1) describe the clinical characteristics of and viruses isolated from patients who presented with neurologic symptoms associated with influenza A infection and were hospitalized at Texas Children's Hospital during October and November 2003 and (2) to raise awareness of the neurologic complications of influenza among US children.**

Methods. **We reviewed the medical and laboratory records of all children who were hospitalized with neurologic symptoms and who also had evidence of influenza virus infection by rapid antigen testing or viral isolation.**

Results. **Eight children aged 5 months to 9 years with neurologic complications associated with influenza A were identified. None of the children had received the influenza vaccine. Four presented with seizures, 3 with mental status changes, and 1 with mutism. All but 1 of the patients had influenza A viral antigen detected in nasal wash samples. Influenza A virus was isolated in culture from nasal wash specimens obtained from 6 of the patients; influenza A virus was also isolated from the cerebrospinal fluid of 1 of these patients. None of the patients had serum metabolic abnormalities or other cerebrospinal fluid abnormalities. Three of the patients had brain imaging abnormalities. Five of the patients were treated with antivirals. All 8 of the patients survived, 6 with complete recovery and 2 with sequelae (1 mild and 1 severe).**

Conclusions. **Neurologic symptoms and sequelae were associated with influenza A virus infection in children during the 2003–2004 influenza season in Houston, Texas. Influenza should be considered in the differential diagnosis in patients with seizures and mental status changes, especially if they present with respiratory symptoms or during an influenza outbreak.** *Pediatrics* **2004;114:e626–e633. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0143;** ***encephalopathy, altered mental status, seizure, viral infection, infectious complication.***

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ABBREVIATIONS. TCH, Texas Children's Hospital; RT-PCR, reverse transcriptase–polymerase chain reaction; CSF, cerebrospinal fluid; EEG, electroencephalogram; MRI, magnetic resonance imaging; CT, computed tomography; RSV, respiratory syncytial virus; HSV, herpes simplex virus; ANE, acute necrotizing encephalopathy; CNS, central nervous system.

Influenza A and B viruses cause influenza epidemics each fall and winter in the United States. Infection typically causes an acute febrile respiratory illness (nonproductive cough, sore throat, nasal congestion, and rhinorrhea) accompanied by headache and myalgias. Children may also experience gastrointestinal disturbances (diarrhea, vomiting, and anorexia).[1] Lower respiratory syndromes such as bronchiolitis, croup, bronchitis, and pneumonia may be severe, and, in rare cases, influenza can progress to life-threatening respiratory compromise, either from the primary infection itself or because of a complicating bacterial superinfection. Other serious complications of influenza include myositis, rhabdomyolysis, and myocarditis. An average of >36 000 influenza-attributable deaths occur during seasonal epidemics in the United States each year.[2] In addition, influenza pandemics have been associated with far greater morbidity and mortality than annual epidemics. For example, the 1918 influenza pandemic is estimated to have caused >20 million deaths worldwide, including >500 000 deaths in the United States.[3] During the 2003–2004 influenza season in the United States, 142 deaths occurred among children.[4]

Neurologic complications associated with influenza have been reported for >100 years. Most recently, epidemic influenza in Japan in the late 1990s was associated with hundreds of cases of encephalopathy among children.[5,6] Although the majority of the patients had relatively minor symptoms, a small but significant number experienced serious complications, resulting in neurologic sequelae and even death. Small numbers of children with neurologic complications have been reported sporadically in Europe and Canada, whereas reports from the United States in the past 60 years have been exceedingly rare.[7–10]

During mid-October to early November 2003, an uncharacteristically early and severe outbreak of influenza A occurred in Houston, Texas. An unusually high number of laboratory-confirmed influenza A cases were medically evaluated and patients were hospitalized at Texas Children's Hospital (TCH), in-

cluding some cases associated with a variety of neurologic symptoms. We report here the largest single-season case series of influenza-associated neurologic complications from an American pediatric center.

METHODS

Patients

Review of medical and laboratory records for this case series was approved by the Institutional Review Board of the Baylor College of Medicine. Children who were hospitalized at TCH and presented with neurologic symptoms associated with influenza A virus infection and were evaluated by ≥1 of the authors during the recent early autumn influenza outbreak were included. Clinical data from medical charts and neuroimaging studies were reviewed. All neurologic examinations were performed by board-certified pediatric neurologists (G.C. and T.E.L.) and/or fellows in the Accreditation Council for Graduate Medical Education –accredited pediatric neurology training program (J.N. and S.M.M.).

Virology

Rapid antigen testing for influenza A and B viruses was performed by the Diagnostic Virology Laboratory at TCH, using a commercially available lateral flow immunoassay[11] (NOW Flu A/B; Binax, Inc, Portland, ME). The test was performed on nasal wash specimens obtained by a standardized protocol using the manufacturer's instructions, with internal kit positive, negative, and procedural controls, as well as external, in-house laboratory controls for each test kit. Results of these rapid tests were reported to clinicians within 2 hours. All specimens submitted for rapid testing were also inoculated for virus isolation onto human foreskin fibroblast, Rhesus monkey kidney, and human lung carcinoma (A549) cell culture monolayers. Viral cultures were inspected daily under light microscopy for cytopathic effect. Hemadsorption with a 0.4% suspension of guinea pig red blood cells was performed on days 2, 5, and 14 of incubation of Rhesus monkey kidney cell cultures. Virus identification and typing of hemadsorption-positive cultures was confirmed by immunofluorescence assay (Chemicon International, Temecula, CA). Influenza A virus isolates were subtyped and antigenically characterized further by the Strain Surveillance Section, Influenza Branch, of the Centers for Disease Control and Prevention (Atlanta, GA), either by hemagglutination inhibition using postinfection ferret antisera to determine antigenic relatedness to known reference strains of influenza A virus or by reverse transcriptase–polymerase chain reaction (RT-PCR) assay.

RESULTS

In October and November 2003, a total of 478 laboratory-proven cases of influenza A were diagnosed at TCH. This early outbreak of influenza was notable for a number of cases with associated central nervous system symptoms (outlined in the case summaries and in Table 1). Neurologic symptoms included encephalopathy and new onset of seizures in previously healthy patients that could not be explained on the basis of metabolic aberrations or by simple febrile illness. Affected patients with previously identified disease processes that could predispose them to neurologic complications of influenza were excluded from this report.

Patient 1

A previously healthy 6-month-old Hispanic boy with age-appropriate development developed a cough and fever to 100.8°F 7 days before admission. This febrile illness progressed to include congestion, decreased appetite, fussiness, and increased sleeping. He was seen by his pediatrician and treated symptomatically with cough syrup and a cool-mist humidifier. Three days before admission, he had a short episode of cyanosis and unresponsiveness. This resolved spontaneously, and no abnormal movements were noted. On the morning of admission, the patient had a generalized tonic-clonic seizure that lasted 1.5 minutes; he was taken to a nearby hospital, where he had 2 similar events. He received lorazepam and phenobarbital and was transferred to the emergency department at TCH. He continued to have several "minor generalized seizures" en route. On arrival, he had a temperature of 104°F and was somnolent but arousable to tactile stimulation, and the respiratory examination was remarkable for increased upper airway noise. Blood and cerebrospinal fluid (CSF) examinations were normal, and electroencephalogram (EEG) and magnetic resonance imaging (MRI) were within normal limits for age. Urine drug screen was positive for previously administered benzodiazepines and barbiturates. Chest radiograph demonstrated a left lower-lobe pneumonia. Influenza A virus was detected by rapid antigen test in a nasal wash specimen and by viral culture in nasal wash and CSF. The patient returned to his normal neurologic baseline within 24 hours of admission and did not have any additional seizure activity. He completed 5 days of cefuroxime and rimantadine, and no additional antiepileptic drugs were given.

Patient 2

A previously healthy 9-year-old black boy with attention-deficit/hyperactivity disorder and otherwise normal development complained of subjective fever, frontal headache, and fatigue on the day before admission. On the morning of admission, he also complained of neck pain and photophobia. Shortly after arising, he experienced a generalized tonic-clonic seizure that lasted for 1.5 minutes, followed by a postictal period first of sleep (for 20 minutes) then of decreased responsiveness and continued photophobia that lasted for 7 to 8 hours. His mental state then returned to normal. His home medications were methylphenidate and dexmethylphenidate, and no recent dosing changes had been made. During emergency medical services transport to TCH, the patient was noted to have a fever of 102°F. On admission, he remained febrile; general examination was remarkable only for a 1–2/6 systolic ejection murmur. On neurologic examination, the patient was alert and oriented and had mild neck stiffness, a positive Brudzinski sign, a negative Kernig sign, and some minor difficulty with tandem gait. A computed tomography (CT) scan of the brain showed decreased size of the sulci, sylvian fissures, and ventricles, and MRI additionally revealed a mild gyral swelling in the left frontal region; both studies were believed to be consistent with a diagnosis of meningoencephalitis. Vancomycin and cefotaxime were administered intravenously on admission. Urine drug screen, CSF viral and bacterial cultures, and respiratory syncytial virus (RSV) rapid antigen test on nasal wash were negative. Rapid antigen test and viral culture from nasal wash were positive for influenza A virus. Oseltamivir was started on day 2 of hospitalization and was administered for 5 days. His mental status re-

TABLE 1. Patient Data Summary

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age	6 mo	9 y	6 y	14 mo	5 mo	5 y	8 y	16 mo
Illness duration before neurologic symptoms	7 d	1 d	2–3 wk	2 d	2 wk	1 d	4 d	3 d
Neurologic presentation	Seizures	HA and seizures	AMS	Seizures	Lethargy	Seizure	Mutism, dysphagia	AMS
Antigen positive (nasal wash)	Y	Y	Y	Y	Y	N	Y	Y
Viral isolation								
Nasal	Y	Y	Y	Y	N	Y	ND	Y
CSF	Y	N	N	N	ND	N	N	N
Viral antigenic characterization	H3N2 A/Fujian/411/2002-like	H3N2 A/Fujian/411/2002-like	H3N2 A/Fujian/411/2002-like	H3N2 A/Fujian/411/2002-like	ND	H3N2 A/Fujian/411/2002-like	ND	H3N2 A/Fujian/411/2002-like
CSF								
WBC	1	4	0	1	ND	6	2	1
Protein, mg/dL	<10	17	<10	14	ND	15	26	58
Glucose, mg/dL	65	81	77	72	ND	67	60	46
LFT, U/L								
ALT	28	25	39	ND	27	ND	ND	101
AST	71	37	43	ND	28	ND	ND	114
Admission WBC	6.45	10.23	7.58	13.72	6.68	12.4	ND	3.88
Segs (bands), %	36	79 (11)	66 (8)	29 (2)	63	71 (1)	ND	36 (9)
Lymphs, %	55	4	19	62	33	20	ND	40
Neuroimaging								
CT	ND	Abnormal	? edema	Normal	ND	Normal	Normal	Abnormal
MRI	Normal	Abnormal	ND	Normal	ND	Abnormal	Normal	Abnormal
Antiviral treatment	Y	Y	Y	Y	N	N	Y	N
Outcome	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Improved	Sequelae

Clinical, laboratory, and imaging findings; treatment; and outcome of patients with neurologic complications associated with influenza. WBC indicates white blood cell; LFT, liver function tests; ALT, alanine transaminase; AST, aspartate transaminase; AMS, altered mental status; HA, headache; N, no; ND, not done; Y, yes.

mained at his normal baseline, but he continued to have a minor headache and increased duration of sleep cycles.

Patient 3

A 6-year-old right-handed black girl with a history of ventricular septal defect (surgical closure at 3 years of age), mild congestive heart failure, and asthma presented with a 2- to 3-week history of intermittent rhinorrhea and cough. On the day of admission, she had a fever to 105°F accompanied by a fluctuating mental status that at times consisted of staring, moving her eyes aimlessly, inability to recognize family members, and incoherence. No seizure activity was noted. In the emergency department, she had 4 episodes of bilious, nonbloody emesis as well as 1 episode of diarrhea, followed by an acute oxygen desaturation into the 80s that responded well to O_2 by nasal canula. There were no complaints of stiff neck, headaches, diplopia, blurred vision, difficulty swallowing, or shortness of breath. The patient's home medications were albuterol and inhaled budesonide for asthma. Temperature on admission was 103.6°F; O_2 saturation was 100% on 10 L of oxygen and 84% on room air. General physical examination revealed intermittent rigors, tonsillar erythema without exudates, and diffuse crackles on lung examination. On mental status testing, the patient was lethargic and irritable but was intermittently able to follow 1-step commands and to recognize close family members. The remainder of the neurologic examination was within normal limits. Blood and CSF tests were normal; urine drug screen, RSV antigen test of nasal wash, and specific CSF studies (herpes simplex virus [HSV] PCR, West Nile, and mycoplasma cultures) were negative. Viral culture of a nasal wash specimen yielded influenza A virus. Chest x-ray was consistent with obstructive airway disease versus aspiration. A CT scan of the head demonstrated sulci, ventricles, and cisterns that were at the lower size limit for age. Nasal wash was positive for influenza A by rapid antigen test. The patient's mental status returned to baseline within 24 hours of admission. The patient received 1 dose of vancomycin, and cefuroxime and acyclovir were administered. Rimantadine was administered on day 2 of hospitalization, and acyclovir was discontinued. The patient completed a 5-day course of rimantadine and was discharged from the hospital 7 days later without neurologic sequelae.

Patient 4

A 14-month-old white girl, previously healthy except for a history of eczema, had a 2-day history of cough, clear rhinorrhea, and fever to 102°F at home. On the morning of admission, she was increasingly lethargic and had poor oral intake. On the way to her pediatrician's office, she had 2 generalized tonic-clonic seizures that lasted 1.5 minutes each, followed by postictal sleepiness. She was noted to be febrile at the physician's office, and ibuprofen was administered. On transport to TCH, she had several short generalized seizures, which she continued to have every 20 to 30 minutes (several of which were not associated with fever) after arrival in our emergency department. The patient was loaded with lorazepam, fosphenytoin, and phenobarbital with cessation of clinical seizure activity. Vital signs on admission were notable for a temperature of 103°F. General examination was remarkable for a maculopapular rash over the trunk and proximal extremities. Neurologic examination demonstrated a lethargic infant with waxing and waning mental status and truncal ataxia. Routine labs and CSF studies were unremarkable. RSV antigen test, CSF viral and bacterial cultures, and enterovirus and HSV PCR of CSF were negative. Nasal wash was positive for influenza A by rapid antigen test, and influenza A virus was isolated from nasal wash culture. CT and MRI scans of the brain were within normal limits. EEG shortly after admission showed multiple electrographic seizure discharges arising from the left central region. Two repeat EEGs over the next 24 hours demonstrated bilateral central spike foci but no seizure activity, and fosphenytoin and phenobarbital were discontinued after 48 hours. However, on the third day of admission, the patient began having multiple tonic-clonic seizures that lasted <30 seconds and did not respond to additional phenobarbital administration. Fever was associated with some but not all of the seizure activity. On day 6 of admission, oxcarbazepine was started and seizure activity stopped. The patient completed a 5-day course of rimantadine and was discharged from the hospital on oxcarbazepine 10 days after admission. She was at her neurologic baseline at the time of discharge.

Patient 5

A 5-month-old white girl with a history of gut malrotation and successful surgical treatment presented with a 2-day history of vomiting and upper respiratory infection. On the day of admission, she was noted to be excessively sleepy and presented to the TCH emergency department. She was believed to be slightly dehydrated but remained lethargic despite adequate rehydration. Over the next 12 hours, the patient did not respond to voice, sternal rub, or painful procedures such as intravenous catheter placement. She then became more responsive and opened her eyes to voice. The neurologic examination was otherwise normal, and her development to date has been normal. Influenza A rapid antigen test on nasal wash was positive. The patient was discharged 2 days after admission at her neurologic baseline.

Patient 6

A 5-year-old right-handed Hispanic boy presented with new onset of seizures. One day before admission, he was noted to have fever, abdominal cramps, and vomiting. On the day of admission, he had a nonfebrile, left focal motor seizure that secondarily generalized with tonic-clonic activity for a total duration of 2 minutes. After recovery from a postictal confused state, his examination was nonfocal. He was empirically started on cefotaxime and acyclovir. Initial EEG demonstrated diffuse slow activity with no occipital dominant rhythm. A noncontrast brain

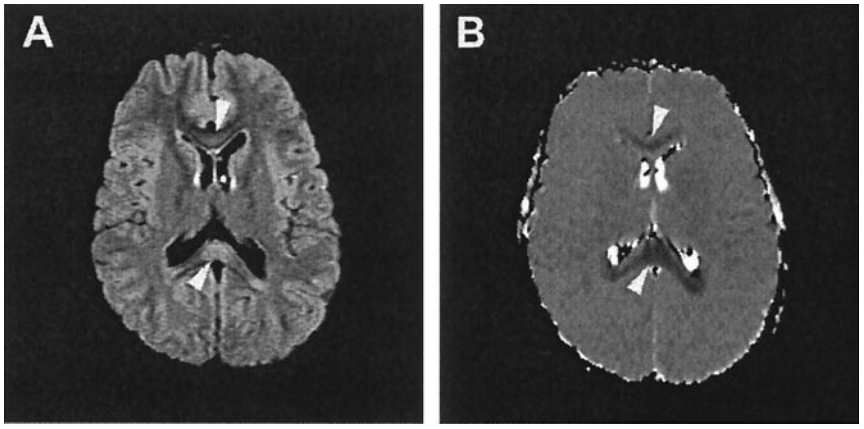

Fig 1. Axial MRI of the brain of patient 6. A, Axial fluid attenuated inversion recovery (FLAIR) image with arrowheads pointing to abnormal signal in the corpus callosum. B, Restricted diffusion on diffusion-weighted imaging shown by arrowheads.

CT on the day of admission was normal. An enhanced MRI scan of the brain obtained 24 hours after the seizure showed bilateral increased T2-weighted and fluid attenuated inversion recovery signal and mild swelling in the hippocampal heads and bodies. In addition, increased T2 signal with restricted diffusion was noted in the splenium and genu of the corpus callosum (Fig 1). These imaging findings were interpreted as likely secondary to the seizure activity, although acute disseminated encephalomyelitis was also noted as a possibility. Rapid antigen testing for influenza was negative, but subsequent culture from a nasal wash specimen identified influenza A. *Mycoplasma*, Epstein-Barr virus, and HSV PCR testing were negative. Serum electrolytes, glucose, renal function studies, and complete blood count were normal. Routine blood, urine, and CSF cultures were negative. Lumbar puncture was traumatic with red cell count of 196; white cell count was 6 with normal protein and glucose. Additional investigations included very-long-chain fatty acid testing, which was normal. The patient had no additional seizures and did not receive anticonvulsants. He was discharged from the hospital with a normal neurologic examination.

Patient 7

An 8-year-old right-handed Hispanic boy with a history of congenital nystagmus and learning difficulties presented with mutism and a gait disorder. Four days before presentation, he had complaints of myalgias and was noted to have a low-grade fever. His pediatrician evaluated him 3 days before admission; rapid antigen testing on nasal wash specimen at that time was positive for influenza A virus. He received a prescription for rimantadine but took only 1 dose. Two days before admission, the parents noted changes in the patient's speech pattern that they characterized as slow and hypophonic. On the day of admission, the patient was completely mute. He additionally had dysphagia and difficulty walking with an unsteady gait. Examination at the time of presentation noted an alert and attentive child with complete mutism. Cranial nerve evaluation revealed a lateral end-gaze nystagmus most notable with extreme leftward gaze. Some drooling was seen with reduced gag, cough, and delayed swallow. The remainder of the cranial nerves were normal. No motor deficits were appreciated, and power was normal in all extremities. Deep tendon reflexes were normal with no pathologic reflexes elicited. Coordination examination showed slowed but accurate rapid alternating movements. His gait, although slowed, was narrow based, and he was able to tandem without difficulty. Sensation was intact to all modalities. CT and MRI scans of the brain were normal. An EEG demonstrated fragmentary brief bursts of generalized, frontocentrally dominant spike and slow wave activity superimposed on a normal background. CSF viral culture and HSV PCR were negative.

Two days into the hospital course, the patient began to show some improvement in his speech, with production of single words, although with hypernasal quality, slowed rate, and low volume. He was able to eat small amounts of pureed food without difficulty. On hospital day 3, he had some mild choreiform movements of the trunk and extremities that were not debilitating. He was discharged from the hospital on hospital day 4. At the time of follow-up evaluation 3 weeks after discharge, his speech was improved, although still slow and low in volume. The remainder of his examination demonstrated the baseline nystagmus and some persistent mild choreiform movements of the fingers on horizontal suspension. Repeat EEG done 3 months after presentation was unchanged.

Patient 8

A 13-month-old Hispanic girl with normal development and a history of 1 previous febrile seizure presented with a 2-day history of fever and generalized status epilepticus in July 2003 that required brief intubation. A head CT scan demonstrated decreased attenuation in the left caudate and bilateral thalami. MRI scan showed extensive increased T2 signal bilaterally in the thalami, caudate nuclei, deep cerebellar nuclei, corpus callosum (genu and splenium), left putamen, hippocampus, and cerebral peduncle (Fig 2 A and B). The lesions did not enhance after administration of contrast. CSF studies and lactate were normal. *Mycoplasma* titers, routine blood and urine cultures, CSF cultures, and HSV and enterovirus PCR were negative. Serum electrolytes, lactate, and hematocrit were also normal. White blood cell count was low (1.69), and alanine transaminase was slightly elevated (138). Urine amino and organic ac-

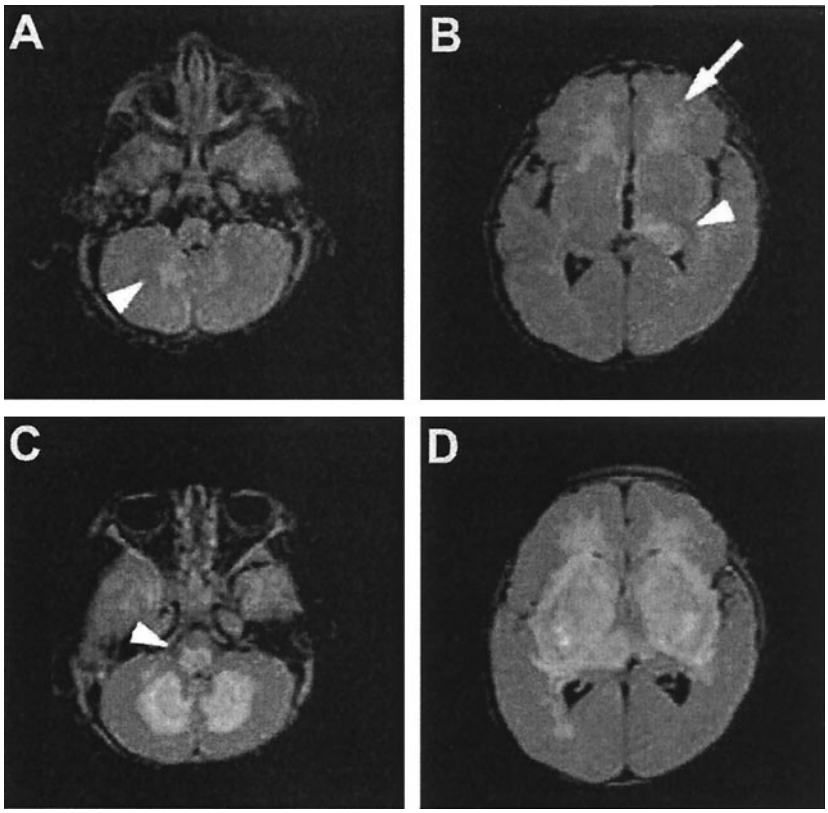

Fig 2. MRI imaging from patient 8. A and B, Axial FLAIR MRI from first admission showing altered signal in deep cerebellar nuclei (A, arrowhead), in frontal white matter (B, arrow), and in thalami (B, arrowhead). C and D, Axial FLAIR MRI from second admission is consistent with a necrotizing encephalitis. Arrowhead in C points to new lesion in the pons.

ids, serum amino acids, free/total carnitine ratio, and mitochondrial DNA analysis were normal. The child was empirically treated with acyclovir, vancomycin, and cefotaxime. Intravenous dexamethasone (4 mg/kg per day for 5 days) was started for presumptive acute disseminated encephalomyelitis. The child improved and was discharged from the hospital at her neurologic baseline. She continued to acquire new skills after discharge.

At 16 months of age (October 2003), the patient developed a 3-day history of fever to 102°F, mild cough, rhinorrhea, somnolence, and irritability, which progressed to emesis, diarrhea, increasing somnolence, and extensor posturing of upper and lower limbs. The posturing persisted despite treatment with benzodiazepines, fosphenytoin, and phenobarbital. She was intubated for airway protection. An MRI scan of the brain revealed diffuse hemorrhage and swelling of the striatum and deep cerebellar nuclei bilaterally, right thalamus, and scattered areas of subcortical frontal and parietal white matter. Extensive edema was seen in the cerebral peduncles, dorsal pons, and medulla (Fig 2 C and D). Magnetic resonance spectroscopy revealed elevated lactate in the basal ganglia. Nasal wash rapid antigen test and subsequent culture were positive for influenza A virus. A stool culture was positive for adenovirus. Additional testing for human immunodeficiency virus, Epstein-Barr virus, enterovirus, HSV, cytomegalovirus, parvovirus B19, mycoplasma, arbovirus, and hepatitis panels was negative. Repeat metabolic testing was unremarkable. She was treated with 5 days of high-dose dexamethasone followed by an oral steroid taper with no clinical improvement. A muscle biopsy of the left vastus lateralis was unremarkable. The child continued to have frequent tonic posturing without associated electrographic seizure activity on EEG. She responded to stimuli only by briefly opening her eyes. A gastrostomy tube was placed for nutritional support. She was discharged from the hospital with a severe static encephalopathy.

DISCUSSION

In his 1918 treatise on the subject, Smith Ely Jeliffe described a wide range of neurologic manifestations associated with influenza, ranging from minor symptoms such as increased fatigue to dire consequences such as coma and death.[12] With the advent of serologic testing, confirmed cases of influenza virus infection (A and B) have been associated with seizures (febrile and nonfebrile),[6,13,14] alterations in mental status ranging from confusion and lethargy to coma,[7,8,15,16] acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome),[17,18] acute disseminated encephalomyelitis,[17] transverse myelitis,[17] abnormal movements,[19] acute psychosis,[20] frontal lobe syndromes,[21] mutism,[9,10] and visual hallucinations.[22] These complications have been reported sporadically in the literature over the past 60 years. Recently, however, hundreds of cases of encephalopathy associated with influenza have been reported in Japan.[6,21,23–25] In these series, a subset of patients (both children and adults) developed a newly described entity termed "acute necrotizing encephalopathy" (ANE).[14,23,26,27] Many patients with this syndrome present with high fever, seizures, and alterations in mental status that rapidly progress to

coma. Brain imaging often demonstrates symmetric white matter, thalamic, basal ganglia, and/or pontine involvement.[28,29] Neuropathologic studies on autopsy tissue show necrosis in these areas, and the lesions are often associated with punctate hemorrhages. Permanent and severe disability or death often result. ANE has been associated with several viruses, but influenza viruses seem to be the most common infectious agent.

All of the neurologic presentations in our cases were associated with influenza A virus infection and were, for the most part, in the milder end of the encephalopathic spectrum. None of the children were Asian in descent. All occurred within 3 weeks of upper respiratory infection symptom onset, with 6 of 8 occurring within the first week. All of the patients also had clinical symptoms and signs of influenza. The timing and concurrent influenzal symptoms suggest that acute influenza caused by the influenza A virus, rather than a "postinfluenza encephalopathy,"[14,16] was responsible for the associated neurologic findings.

Seizures were the most common neurologic symptom in our patients and were seen in 4 of 8 patients. However, we do not believe that the seizures seen in these cases can be explained simply as febrile seizures. Three of our patients (1, 2, and 6) had laboratory and/or imaging evidence of central nervous system (CNS) involvement. Influenza A virus was isolated from the CSF of patient 1; patient 2 is 9 years old, and patient 6 is 5 years old, making a first episode of febrile seizures unlikely; and patients 2 and 6 had brain imaging studies suggestive of direct CNS involvement. Finally, patient 4 experienced recurrent seizures 3 days after the first seizure, and several of these were in the absence of fever. Although we do not believe fever to be the cause of seizures in these children, it has been reported that influenza virus infection is more commonly associated with febrile seizures in children than are other viral infections.[13] The mechanism by which this occurs is currently unknown.

Patient 8's neurologic problems could have been attributable to a metabolic or mitochondrial disorder that was exacerbated by influenza; the similar previous episode that was associated with multiple brain lesions on MRI supports this contention. However, extensive evaluations for other infectious and metabolic causes, including a muscle biopsy, were negative, and the second episode was clearly associated with influenza A virus infection. We believe that this patient's second presentation is best explained as influenza-associated ANE, representing only the second such report from the United States.[30] The only other associated infectious finding was the isolation of adenovirus in the child's stool at the second presentation. It is interesting that Steininger et al[14] reported a possible association between adenoviral infection and postinfluenzal encephalopathy after influenza A virus infection. Our patient's first episode was also associated with a possible viral prodrome. There are reports of children having multiple episodes of influenza-related ANE.[28] Whether these represent true viral syndromes or a currently undetectable inborn metabolic derangement manifesting under stress is an open question. Regardless, it is important to recognize that influenza virus infection can trigger such a response, even in the absence of CNS infection.

It has been postulated that influenza encephalopathy might be related to metabolic disturbances that occur in relation to the primary infection. In support of this argument, influenza, particularly caused by influenza B virus infection, has been associated with the occurrence of Reye's syndrome in children exposed to aspirin.[31] None of our patients had a history of aspirin administration, and, in the cases in which liver enzymes were analyzed, none had evidence of hepatic failure. This, coupled with the clinical presentations and subsequent improvement in the majority of cases, makes it highly unlikely that any of these patients had Reye's syndrome.

The pathogenic mechanism of influenza virus infection on the nervous system remains a topic of debate. In fact, very few studies have shown the presence of viral antigens in CNS tissue at autopsy, and isolation of virus from CSF has been equally rare. All 8 of the cases in this series had influenza A virus detected in respiratory specimens. However, we were able to culture influenza A virus from the CSF of only 1 patient (patient 1). Recently, RT-PCR techniques have been used to test for the presence of viral RNA in serum and CSF samples; however, these techniques have met with varied success, and the majority of studies have been unable to provide direct evidence of influenza virus infection in CNS sites.[10,14] RT-PCR for influenza A viral RNA was not done on any of the CSF samples in this case series because priority was given to viral culture techniques, leaving insufficient quantities for PCR.

Influenza A virus strains with certain hemagglutinin (H) and neuraminidase (N) profiles are more often associated with CNS complications. In particular, influenza A (H3N2) virus infections have been found in the majority of encephalopathy cases reported in Japan and Europe, although occasionally influenza A (H1N1) viruses have been isolated as well. All of the viral isolates (from patients 1–4, 6, and 8) in this series were antigenically characterized as A/Fujian/411/2002(H3N2)-like. This strain is an antigenic drift variant of the influenza A (H3N2) vaccine strain, A/Panama/2007/99 (H3N2)-like. Whether the association between certain influenza A virus strains and neurologic complications results from an undetected tropism of these strains for the CNS or a greater likelihood of causing a host reaction that leads to encephalopathy remains unknown.

It is unknown whether influenza vaccination would have prevented or attenuated the neurologic complications associated with influenza A virus infection in the reported cases. Four of the 8 children were in a high-risk group currently recommended for influenza vaccination.[32] However, none of the patients was vaccinated, and most of them presented before the influenza vaccine was widely available in the Houston area. In addition, the 2003–2004 influenza vaccine did not include the A/Fujian/411/2002 (H3N2)-like strain, which was the predominant

strain associated with the epidemic and identified in 6 of the cases.

Of equal ambiguity is the utility of antiviral treatments on the course or outcome of influenza-associated encephalopathy or encephalitis. Efficacy of antivirals for reducing the symptoms, signs, and duration of acute uncomplicated influenza (respiratory disease) has been established. No randomized, controlled study has examined the impact of antiviral treatment on influenza-associated CNS manifestations, although the use of antivirals in some neurologic complications of influenza has been reported.[5,10,33] Several of the patients in our series were treated with a full course of antiviral medication (rimantadine or oseltamivir). It is not clear whether this intervention resulted in any clinical improvement or whether the neurologic symptoms were self-limited. It seems reasonable to recommend antiviral therapy at this time, but additional studies are needed to evaluate its true role in the treatment of influenza-related encephalopathy.

In summary, we report 8 influenza A cases that were associated with encephalopathy syndromes during a severe influenza outbreak in Houston, Texas. Our experience with influenza during the fall of 2003 was similar to that reported in previous years in Japan but distinctly different from our previous experience. Whether this reflects the virulence of the predominant influenza strain A/Fujian/411/2002 (H3N2)-like or whether high attack rates resulted in the identification of a number of uncommon neurologic complications is unknown. Influenza-associated encephalopathy should be considered in the differential diagnosis for children who present with new-onset seizures or mental status changes during the influenza season.

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