MAJOR ARTICLE

Encephalitis Associated with Influenza B Virus Infection in 2 Children and a Review of the Literature

Jason G. Newland,[1,2] José R. Romero,[1,2,3,4] Meera Varman,[3] Casey Drake,[2,4] Amy Holst,[2,4] Tom Safranek,[5] and Kanta Subbarao[6,a]

[1]Department of Pediatrics, University of Nebraska Medical Center, [2]Department of Pediatrics, Creighton University, [3]Combined Division of Pediatric Infectious Diseases, University of Nebraska Medical Center and Creighton University, [4]Children's Hospital, Omaha, and [5]Nebraska Health and Human Services, Lincoln, Nebraska; and [6]Influenza Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

Two children with influenza B–associated encephalitis (IBAE) presented to our hospital during the winter of 2000–2001, both of whom had cases notable for mutism in association with encephalitis. A review of the literature identified 13 additional reports consistent with IBAE that contained sufficient data for analysis. Eleven of 15 reported cases occurred in children aged ≤18 years; of these, more than one-half occurred in children <11 years of age. Neurologic symptoms appeared within the first 4 days of illness in 13 cases. Speech abnormalities were observed in 4 patients and consisted of mutism in 3. Although the majority of patients recovered fully, 3 were left with neurologic sequelae, and 1 died. These cases reveal the spectrum of IBAE and its potential for long-term sequelae. Clinicians caring for children should remain vigilant for this rare complication of influenza B virus infection.

Influenza viruses are segmented, negative-sense, single-stranded RNA viruses in the family Orthomyxoviridae [1]. They are divided into 3 distinct types on the basis of antigenicity: A, B, and C. Influenza viruses are responsible for annual winter epidemics of infection worldwide that result in significant morbidity and mortality [2]. In healthy adolescents and adults, influenza A and B viruses primarily cause a self-limited upper respiratory tract infection characterized by abrupt onset of fever and chills in association with headache, cough, sore throat, and myalgias [3]. Complications from influenza A or B virus infection include pneumonia, myositis, myocarditis, and encephalitis.

The clinical presentation in infants and children may be more varied than that in older patients [3]. In addition to the previously described symptoms, diarrhea, vomiting, and anorexia are more commonly observed. Influenza-associated respiratory syndromes in children may include croup, bronchiolitis, or bronchitis. Additional presentations in this age group include nonspecific febrile illness, febrile seizures, and a sepsislike syndrome.

Although encephalitis has been associated with both influenza A and B virus infection, this complication appears to be less frequent with type B infections. During the winter of 2000–2001, two children presented to Children's Hospital (Omaha, NE) with evidence of encephalitis associated with influenza B virus infection. This report describes these 2 patients and reviews the findings for cases of influenza B–associated encephalitis (IBAE) reported in the medical literature.

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[a] Present affiliation: Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.

Reprints or correspondence: Dr. José R. Romero, Combined Div. of Pediatric Infectious Diseases, UNMC/CU, 2500 California Plaza, Criss II, Rm. 409, Omaha, NE 68171 (jrromero@unmc.edu).

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MATERIALS AND METHODS

Literature review. The MEDLINE database was searched to identify reported cases of IBAE using the discriminators "influenza B" and "encephalitis." The reference sections of reports so identified were further scrutinized for additional case reports. All reports were reviewed, and cases with clinical presentations suggestive of Reye syndrome [4] were excluded from analysis. The remaining cases formed the basis for this review. Institutional review board approval for review of medical records was granted from Children's Hospital.

Nucleic acid amplification. RNA was extracted from 140 μL of CSF and eluted in 60 μL of water with use of the QIAamp Viral RNA Mini Kit (Qiagen). RT-PCR for amplification of influenza A virus– and influenza B virus–specific genes was performed with 2.5 μL of RNA in 50 μL of Promega Access RT kit reaction. Three separate primer pairs designed to amplify the *NP* gene of influenza A viruses (A/NP F1 and A/NP R1143), the *NP* gene of influenza B viruses (B/NP F275 and B/NP R1320), and the *HA* gene of influenza B viruses (B/HA F25 and B/HA R1140) were used (table 1). The cycling conditions were as follows: an RT step of 45 min at 48°C followed by denaturation at 94°C for 7 min. This was followed by 40 cycles of 94°C for 30 s, 48°C for 1 min, and 68°C for 2 min. An extension step of 7 min at 68°C was performed at the end of the cycling. The product from the first round of PCR was purified through a QIAquick column (Qiagen), and 2.5 μL of DNA from each reaction was used for nested PCR with primer pairs A/NP F301 and A/NP R927, B/NP F402 and B/NP R1129, and B/HA F36 and B/HA R759. The PCR products were electrophoresed through a 1% agarose gel, and DNA was visualized with ultraviolet light on an ethidium bromide–stained gel.

Table 1. Primers used in RT-PCR detection of influenza genome.

Primer	Sequence
B/NP F275	5′-AAC CAG ATG ATG GTC AAA GCT-3′
B/NP F402	5′-GAA TGC CAG AGA TGT CAA AGA-3′
B/NP R1129	5′-AAT ATG GAA ACA GGT GTT GCC-3′
B/NP R1320	5′-AGC TTG ATG GAC ATC AGA GCT-3′
A/NP F1	5′-ATT CTA CAT CCA AAT GTG CAC-3′
A/NP F301	5′-GGA AAG ATC CTA AGA AAA CTG-3′
A/NP R927	5′-TCT TTT TCG AAG TCG TAC CCA CTG-3′
A/NP R1143	5′-AGC AAT TTG TAC TCC TCT AGT-3′
B/HA F25	5′-ATC CAC AAA ATG AAG GCA-3′
B/HA F36	5′-GAA GGC AAT AAT TGT ACT-3′
B/HA R759	5′-GCC GCC AAT CTG AGA AAC-3′
B/HA R1140	5′-ACC AGC AAT AGC TCC GAA-3′

CASE REPORTS

Patient 1. A 3-year-old white girl presented with lethargy, mental status changes, and fever of 2 days' duration. On the morning before admission to the hospital, the patient developed a temperature of 38.3°C (101°F), which persisted throughout the day and was associated with decreased activity. The next morning, she fell as she attempted to get out of bed and was unable to stand without assistance. En route to the hospital, she was awake but unresponsive to verbal stimuli. At admission to the emergency department, her vital signs were as follows: temperature, 38.3°C (101°F); heart rate, 128 beats/min; respiratory rate, 20 breaths/min; and blood pressure, 107/83 mm Hg. Physical examination revealed cool and mottled extremities with a 3–4-s capillary refill. She received normal saline (20 mL/kg) and intravenously administered ceftriaxone. A complete blood cell count revealed 7700 WBCs/mm^3 (60% granulocytes, 27% lymphocytes, and 13% monocytes). Her hemoglobin level was 12.3 mg/dL, her hematocrit was 41%, and her platelet count was 225,000 platelets/mm^3. Analysis of a CSF specimen obtained via lumbar puncture revealed an RBC count of 3 cells/mm^3 and a WBC count of 5 cells/mm^3, with 74% neutrophils and 26% lymphocytes. The CSF protein level was 18 mg/dL, and the glucose level was 45 mg/dL. The findings of a chemistry and disseminated intravascular coagulation panel were normal, except for an aspartate aminotransferase level of 93 IU, an alanine aminotransferase level of 63 IU, and a glucose level of 56 mg/dL.

After transfer to the general pediatric ward, the patient's temperature was 38.8°C (101.9°F), her heart rate was 156 beats/min, her respiratory rate was 34 breaths/min, and her blood pressure was 120/59 mm Hg. Physical examination revealed an awake, cooperative, photophobic girl who was unresponsive to verbal stimuli. She responded to tactile and noxious stimuli, her deep tendon reflexes were normal in all extremities, and Brudzinski's, Kernig's, and Babinski's signs were absent.

Approximately 3 h after admission to the ward, the patient's mental status deteriorated, and decorticate posturing, nystagmus, dysconjugate gaze, and absence of patellar reflexes were observed. CT of her head revealed diffuse cerebral edema. An electroencephalogram revealed diffuse slowing consistent with encephalopathy. After transfer to the pediatric intensive care unit, she underwent intubation, and mannitol was administered. Empirical therapy with acyclovir, erythromycin, ceftriaxone, and vancomycin was initiated. A nasopharyngeal aspirate was obtained, and influenza B virus was identified by direct fluorescent antibody assay and, subsequently, cell culture. Oseltamivir was administered orally at a dosage of 2 mg/kg twice per day for 7 days.

Blood, CSF, and urine cultures remained sterile. The results of serologic assays for antibodies to Epstein-Barr virus, mycoplasma, cytomegalovirus, and *Bartonella henselae* were negative. Herpes simplex virus and enterovirus genomes were not

Table 2. Demographic and clinical characteristics of patients with influenza B encephalitis.

Patient	Ref.	Age in years, sex	Fever	Days to onset of neurologic symptoms	Neurologic findings	Seizures	Neuroimaging findings	EEG findings
1	[5]	38, M	NA	14	Headache, dizziness, photophobia, parasthesias, somnolence, diplopia, EOM paresis, sluggish pupils, BLT ptosis, absent DTRs, Babinski's sign absent	NA	NA	NA
2	[5]	18, F	NA	1	Headache, extreme lassitude, diplopia, sluggish pupils, right-side ptosis, right–eye muscle weakness, nuchal rigidity, decreased DTRs	NA	NA	NA
3	[6]	9, M	+	4	Coma, urinary incontinence, right eye deviation, left-side hemiparesis, left Babinski's sign present	+	Normal right carotid angiography	NA
4	[6]	6, F	+	3	Abnormal behavior, semiconscious progressing to unconscious, pupils unresponsive, bulbar paralysis, brisk then absent DTRs, Babinski's sign present	NA	NA	NA
5	[7]	16, F	+	0	Bifrontal headache, syncope, ocular muscle weakness in abduction in left eye greater than right eye, right-side papilledema, nuchal rigidity, and Kernig's, Brudzinski's, and Babinski's signs present	NA	NA	NA
6	[8]	37, F	+	0	Disoriented, unresponsive to verbal stimuli, semipurposeful movements to pain, nuchal rigidity, increased muscle tone and DTRs, and Kernig's and Babinski's signs present	Status epilepticus	Normal CT and nuclear scan	Loss of α rhythm with widespread δ activity
7	[8]	38, F	+	4	Headache, confusion, stuporous, dysphasia, unresponsive to verbal stimuli, eyes deviated to left, nuchal rigidity, right arm paresis and decreased DTR	Generalized	Normal CT	Low frequency activity posterior temporal region
8	[9]	41, M	+	7	Headache, confusion, disorientation, unresponsive to verbal stimuli progressing to unresponsive to painful stimuli, nuchal rigidity, Babinski's sign absent	Generalized	Normal CT and MRI	NA
9	[10]	<2,[a] M	NA	2	NA	Generalized	NA	NA
10	[11]	6, F	+	2	Ataxia, somnolence, mutism, lethargy, delirium, agitation, emotional lability, few purposeful movements	NA	Normal CT and MRI	NA
11	[12]	18, F	+	3	Coma, meningeal signs absent, increased DTRs, Babinski's sign present	Focal and generalized	Initial CT and MRI normal; MRI from day 32 revealed left-side hippocampal intensity	Periodic lateralized epileptiform discharges left hemisphere
12	[13]	6, F	+	2	Loss of consciousness, nuchal rigidity absent, Kernig's sign absent	Generalized	Normal CT	NA
13	[14]	10, M	+	3	Lethargy, coma, decreased muscle strength, meningismus absent, decreased DTRs, Babinski's sign present	NA	Normal MRI	NA
14	PR	3, F	+	2	Ataxia, mutism, coma, decorticate posturing, photophobia, and Brudzinski's, Kernig's, and Babinski's signs were absent	−	Initial CT revealed cerebral edema; follow-up MRI was normal	Diffuse slowing
15	PR	4, M	+	1	Headache, somnolence, urinary incontinence, mutism, Brudzinski's sign present, Kernig's and Babinski's signs absent	−	Normal CT	Diffuse slowing

NOTE. BLT, bilateral; DTRs, deep tendon reflexes; EEG, electroencephalogram; EOM, external ocular muscle; NA, data not available; PR, present report; ref., reference; +, positive or present; −, negative or not present.

[a] Twenty-two months old.

Table 3. Laboratory findings and outcome for patients with influenza B encephalitis.

Patient	Ref.	CSF values				Influenza B genome present	Influenza viral culture specimen (result)	Influenza B serologic assay result	Additional tests (results)	Outcome
		Cell count, cells/mm^3	Cell differential	Glucose, mg/dL	Protein, mg/dL					
1	[5]	4	NA	NA	30	NP	NA	NA	—	Sequelae: diplopia, BLT EOM weakness, areflexia, hip and right wrist weakness
2	[5]	8	"Lymphocytes"	NA	20	NP	NA	NA	—	Complete resolution
3	[6]	1	NA	79	20	NP	Throat (+), nasal (+)	CF D5, 1:8; CF D17, 1:16; HAI D5, <1:10; HAI D17, 1:40	—	Complete resolution
4	[6]	5	NA	65	15	NP	Throat (+), nasal (+)	CF D7, <1:8	RSV titer, 1:512	Fatal; death on day 8
5	[7]	Normal	NA	Normal	Normal	NP	Nasopharyngeal (+)	NA	—	Complete resolution
6	[8]	1st LP, 43 WBCs, 6700 RBCs; 2nd LP, 75 WBCs, 584 RBCs	1st LP, Ls; 2nd LP, Ls	1st LP, 27	2nd LP, 32	NP	NA	CF D5, <1:10; D16, 1:320; HAI D5, <1:10; D16, 1:80	Serologic tests for HSV, influenza A, measles, mycoplasma, mumps, VZV (−)	Complete resolution
7	[8]	Normal	NA	NA	NA	NP	NA	CF D2, 1:80; CF D16, 1:1280; HAI D2, <1:10; HAI D16 1:40	Serologic tests for HSV, influenza A, measles mumps, VZV (−)	Complete resolution
8	[9]	1st LP, 6 WBCs; 2nd LP, 21 WBCs	1st LP, 80 Ls, 20 Ms; 2nd LP, 77 Ls, 20 Ms, 3 Ns	1st LP, 81; 2nd LP, 79	1st LP, 54; 2nd LP, 65	NP	Nasopharyngeal (−), CSF (−)	CF D1, 1:16; CF D18, 1:64	Serologic tests for HSV, influenza A, mumps (−); bacterial cultures of blood, CSF, and urine specimens (−)	Complete resolution
9	[10]	NA	NA	NA	NA	–	Throat (+)	HAI D1, <1:32; HAI D14, 1:128	—	Not reported

10	[11]	22 WBCs	96 Ls, 4 Ms	63	28	+	Nasopharyngeal (+), CSF (−)	CF D1 1:8; CF D43, 1:64	Serologic tests for arbovirus, *Bartonella* species, EBV, VZV (−); bacterial and fungal culture of CSF specimens (−); HSV PCR (−)	Sequelae: continued ataxia, and cognitive difficulty
11	[12]	1 WBC	1 L	145	25	NP	Throat (−), serum (−), CSF (−)	CF D1, 1:128; CF D13, 1:16; HAI D112, 1:2048	Serologic tests for CMV, Japanese encephalitis, influenza A, measles, parainfluenza 1 and 2, mumps, VZV (−); HSV PCR (−)	Complete resolution
12	[13]	0	NA	145	28	NP	Nasopharyngeal (+)	HAI D16, 1:2048	Blood glucose level, 400 mg/dL	Complete resolution
13	[14]	1st LP, 15 WBCs; 2nd LP, 18 WBCs	2nd LP, 17 Ns, 85 Ls	1st LP, 79; 2nd LP, 82	1st LP, 17; 2nd LP, 28	+	Nasopharyngeal (+), CSF (−)	—	Bacterial cultures of blood, CSF, and urine specimens (−)	Complete resolution
14	PR	5 WBCs, 3 RBCs	74 Ns, 26 Ls	45	18	−	Nasopharyngeal (+)	—	Serologic tests for *Bartonella* species, CMV, EBV, mycoplasma (−); bacterial culture of blood, urine, and CSF specimens (−); enterovirus PCR (−); HSV PCR (−)	Sequelae: continued oromotor apraxia
15	PR	130 WBCs, 6990 RBCs	8 Ns, 28 Ls, 64 Ms	63	39	NP	Nasopharyngeal (+)	—	Bacterial cultures of blood, CSF, and urine specimens (−)	Complete resolution

NOTE. BLT, bilateral; CF, complement fixation; D, day; EBV, Epstein-Barr virus; EOM, external ocular movements; HAI, hemagglutination inhibition; HSV, herpes simplex virus; L, lymphocyte; LP, lumbar puncture; M, monocyte; N, neutrophil; NA, not available; NP, RT-PCR not performed; PR, present report; ref., reference; RSV, respiratory syncytial virus; VZV, varicella zoster virus; +, positive or present; −, negative or not present.

amplified from the CSF specimen. Glucose and ammonia levels were 180 mg/dL and 9 μm/L, respectively. The results of an acyl carnitine profile and a urine toxicology screen were negative.

The patient underwent extubation on the fourth day of hospitalization. Physical examination on the sixth day of hospitalization demonstrated truncal ataxia, weakness, and mutism. MRI of her brain performed 14 days after admission revealed resolution of the cerebral edema. She remained hospitalized for 21 days. At the time of discharge from the hospital, the patient was able to sit without assistance and to grasp objects, and her ability to walk had improved. However, her expressive language skills remained severely delayed, and she was unable to follow 3-step simple commands. Approximately 1 month after discharge, all of her motor abnormalities had resolved, but speech remained abnormal. Approximately 2.5 months after discharge, she continued to have difficulty with coordinating her phonatory/respiratory systems, finding words, and following 3-step commands.

Patient 2. A 4-year-old white boy was hospitalized with a 4-day history of emesis, diarrhea, and fever. Two days before admission to the hospital, he developed extreme lethargy, was unresponsive to verbal stimuli, and became incontinent. On the second day of hospitalization, he developed a temperature of 38.9°C (102°F), back pain, and a right-side occipital headache. He was transferred to Children's Hospital. At admission, his vital signs were as follows: temperature, 38.2°C (100.7°F); heart rate, 132 beats/min; respiratory rate, 30 breaths/min; and blood pressure, 101/50 mm Hg. Physical examination revealed a stuporous boy with brief moments of lucency. During these moments of lucency, he would follow commands but was unable to speak. Brudzinski's sign was present, deep tendon reflexes were normal, and Babinski's sign was absent. Analysis of a CSF specimen obtained by traumatic lumbar puncture revealed an RBC count of 6990 cells/mm^3 and a WBC count of 130 cells/mm^3 (8% neutrophils, 28% lymphocytes, and 64% monocytes). The CSF protein level was 39 mg/dL, and the glucose level was 63 mg/dL. The serum ammonia level was <0.1 μm/L. A complete blood cell count revealed a WBC count of 7800 cells/mm^3, a hemoglobin level of 13.1 mg/dL, hematocrit of 39%, and a platelet count of 179,000 platelets/mm^3. CT of the head, with and without contrast, revealed nothing abnormal. A nasopharyngeal aspirate was obtained, and influenza B virus was detected by direct fluorescent antibody assay and, subsequently, cell culture. Blood, CSF, and urine cultures were sterile. An electroencephalogram was remarkable for diffuse slowing consistent with encephalopathy. Oseltamivir (2 mg/kg) was administered orally twice per day for 5 days. The patient became more alert the day after the transfer to Children's Hospital. He continued to improve, and he was discharged from the hospital without neurologic sequelae after a total of 6 days in the hospital.

RESULTS

In the English-language literature, 21 cases of IBAE have been reported [5–20]. Eight cases were excluded from this analysis: 4 were reported in articles that contained insufficient information for analysis [15–18], 3 were reported in studies that failed to provide adequate serologic or cell culture–based evidence of influenza B virus infection [6, 19], and one case may have been Reye syndrome [20]. Therefore, including the 2 patients in this report, a total of 15 patients had cases that met clinical criteria for IBAE. Their histories and clinical and laboratory findings are summarized in tables 2 and 3, respectively.

Sex and age were provided for all 15 patients. Nine female and 6 male patients were described. Ages ranged from 22 months to 41 years, with a median of 9 years. Of the 15 cases, 11 (73%) occurred in children ≤18 years of age, and 8 patients (53%) were <11 years of age.

In 13 cases, infection was confirmed by serologic or virologic methods. Seven of 9 patients for whom serologic studies were performed had titers indicative of influenza B virus infection, as determined by hemagglutination inhibition or complement fixation. Virus was detected in the respiratory tract in 9 of 12 patients for whom virus isolation was attempted.

The onset of neurologic signs and symptoms occurred within the first 4 days of illness in 13 (87%) of 15 patients, and onset occurred in all cases by the 14th day of illness. The reported neurologic findings among the cases were diverse (table 4). Speech abnormalities were reported in 4 patients; these took the form of mutism in 3 patients (patients 10, 14, and 15), all of whom were ≤6 years of age.

Table 4. Summary of neurologic signs and symptoms in patients with encephalitis associated with influenza B virus infection.

Neurologic finding	No. of patients
Seizures	7
Nuchal rigidity	6
Abnormal deep tendon reflexes	7
Speech abnormalities	4
Mutism	3
Dysarthria	1
Coma	5
Babinski's sign	6
Brudzinski's sign	2
Kernig's sign	2
Urinary incontinence	2

CSF specimens were analyzed for 14 patients. Lymphocytic pleocytosis (lymphocyte count range, 8–130 lymphocytes/mm^3) was observed in 5 patients. CSF glucose and protein concentrations were normal in all patients. Three of 5 patients had elevated intracranial pressure. One patient had an opening pressure of 24 cm H_2O (patient 1). A second patient's (patient 5) CSF specimen initially overflowed the manometer, and a closing pressure of 25 cm H_2O was noted. The final patient (patient 14) had evidence of cerebral edema on CT scan.

In 6 patients, an attempt was made to detect the presence of influenza B virus in the CNS. In 4 patients, virus isolation from the CSF via cell culture was unsuccessful. RT-PCR amplification of influenza B viral genome from the CSF was attempted in 4 patients, including one of ours. Influenza genome was successfully amplified on day 3 of illness in 2 patients (patients 10 and 13).

Imaging of the brain was performed for 9 patients (CT for 4 patients, MRI for 1, and both MRI and CT for 4). No abnormalities were noted during the initial examinations for all patients except the aforementioned patient 14. Electroencephalograms were obtained for 5 patients (patients 6, 7, 11, 14, and 15); all patients had abnormal findings, which consisted of diffuse slowing, low-frequency activity in the left posterior temporal region, and transient periodic lateralized epileptiform discharges.

In general, the clinical outcome was favorable. For 10 of the 14 patients for whom the clinical outcome was provided, neurologic signs and symptoms completely resolved, and the patients' functions returned to normal. Three patients experienced neurologic sequelae consisting of paresis of extraocular muscles (patient 1), ataxia and new-onset cognitive difficulties (patient 10), or difficulty with rhythmic speech (patient 14). The sole patient who died had concurrent infection with respiratory syncytial virus, as determined by rising titers (patient 4).

DISCUSSION

Encephalitis is a rare complication of influenza infection. The earliest report of possible influenza-associated encephalitis involved an epidemic of infection in 1712 in Tübingen, Germany [21]. These cases were characterized by "sleepiness and marked cerebral symptoms" [21]. During the H3N2 influenza A pandemic of 1890, cases of "lethargy with delirium" were reported in northern Italy. This condition was termed "nona" by the lay public [21]. It was not until the 1957–1958 H2N2 pandemic that a strong causal link was established between influenza A virus infection and encephalitis with a report documenting virus isolation or specific antibody responses in patients with influenza-associated encephalitis [22].

Most recently, reports from northern Japan describe several infants and children with acute encephalitis or encephalopathy associated with the H3N2 strain of influenza A virus [23, 24]. These reports are striking because of the high associated mortality and morbidity rates [23]. In some subjects, the amplification of influenza virus genes was reported from the CSF [10, 11, 14, 23–25]. However, other investigators have not reported similar success in the amplification of influenza genome in the CSF [26].

The association of influenza B virus with encephalitis was first documented in 1946 during an epidemic of influenza B virus infection in London [5]. However, in neither of the 2 cases in that report was conclusive evidence of influenza B virus infection provided by virus isolation or serologic testing. It was not until 1966 that the first cases of IBAE confirmed by virus isolation and serologic testing were reported [6].

During the 2000–2001 influenza season, we encountered 2 patients (patients 14 and 15) with encephalitis associated with culture-documented influenza B virus infection; both infections involved B/Sichuan/379/99-like strains, the predominant circulating strain of influenza B virus. This strain was responsible for 41% of all influenza isolates identified by the Centers for Disease Control and Prevention (Atlanta, GA) during the winter of 2000–2001 [27]. An additional 13 cases of IBAE were identified from a review of the medical literature.

Although Reye syndrome has been associated with epidemics of influenza B virus infection, it is improbable that either of the patients we describe experienced this entity. Both patients lacked the clinical history typical of Reye syndrome, and neither patient had a history of aspirin use [4]. In addition, the temporal relationship between the onset of neurologic symptoms and onset of their illnesses was shorter than that commonly seen in patients with Reye syndrome. Furthermore, evidence of hyperammonemia and markedly elevated liver transaminase levels were not found [4]. Although patient 14 had mild hypoglycemia, this could be explained by poor oral intake.

In 13 of the reported cases of IBAE, the onset of neurologic symptoms occurred within 4 days of the onset of fever. This finding is reminiscent of the cases reported by Togashi et al. [23], who noted that the mean time to onset of neurologic symptoms from the onset of fever was 1.9 days. Although the pathophysiological mechanisms of IBAE are not well understood, the early onset of neurologic symptoms may argue against a postinfectious etiology. Experimental evidence from murine models indicates that some influenza A strains are capable of invading the CNS [28–30]. However, these experiments were performed with a mouse-adapted neurotropic strain of influenza A virus that had been passaged extensively in the laboratory.

Although there are recent reports indicating that influenza A and B viral genes are present in the CSF of patients with encephalitis [10, 11, 14, 23, 24], other investigators suggest that

the detection of influenza genome in the CSF is an uncommon event [25, 26]. Our attempts to amplify influenza B viral genes from a CSF specimen obtained from one of our patients were unsuccessful when nested primer pairs directed against the *NP* and *HA* genes were used. Only one report has documented successful virus isolation of influenza B virus from CSF. Unfortunately, this patient was excluded from this analysis as a result of insufficient clinical data [15].

A salient finding of this review was the preponderance of cases of IBAE that occurred in children and adolescents. Of these patients, 8 were ⩽10 years of age. One possible explanation for this clustering of cases among children maybe that a less severe illness is manifested by adults as the result of previous exposure to influenza B viruses resulting in partial immunity to influenza B virus infection [31, 32].

Our analysis of the neurologic signs and symptoms is confounded by the lack of uniformity in reporting. Therefore, it must be borne in mind that the reported neurologic abnormalities (table 4) may be an underrepresentation of their true occurrence and diversity. An unexpected finding of this review was the association between IBAE and speech abnormalities in approximately one-quarter of the reported cases. In 3 of 4 cases, this took the form of mutism, a heretofore unrecognized association. The long-term outcome for these patients was generally favorable, and only one patient (patient 14) had long-term speech impairment. Seven patients were reported as having seizures described as predominantly generalized; all recovered completely. Febrile seizures have been reported in association with influenza A and B virus infection in children [15, 33]. During a 2-year period, the average incidence of febrile seizures associated with influenza A virus infection in Hong Kong was ~19% [33].

The findings of CSF analysis were found to be normal in the majority of cases. Increased intracranial pressure was documented in only 3 patients. Cytochemical abnormalities, when present, tended to be limited to mild CSF pleocytosis with a predominance of mononuclear leukocytes. The degree of pleocytosis observed was similar to that reported for influenza A–associated encephalitis [10]. Cerebral imaging was performed during the acute phase of IBAE for 9 patients, and in only one patient (patient 14) was an abnormality observed, consisting of diffuse cerebral edema. In contrast, MRI or CT abnormalities appear to be more frequently documented in patients with influenza A–associated encephalitis [34–36].

Oseltamivir has been shown to modify the course of influenza infection in children [37]. Although oseltamivir was administered to both of our patients, we could not document evidence that this therapy aided in their recovery. A recent report failed to demonstrate the presence of oseltamivir or its metabolite, oseltamivir carboxylate, in the CSF after administration to a patient with IBAE [14]. This finding calls into question whether oseltamivir is likely to be of benefit in the therapy of influenza-associated encephalitis if, in fact, influenza viruses invade the CNS.

Although it is more than likely that the 15 cases of IBAE summarized in this review are an underrepresentation of the true occurrence of this complication, several conclusions can be drawn from this analysis. IBAE appears to occur predominantly in children. The onset of neurologic symptoms tends to occur within the first 4 days of the illness. Abnormalities found via cerebral imaging appear to be unusual, which is not the case for influenza A–associated encephalitis. Although the majority of patients with IBAE recover fully, neurologic sequelae and fatalities have been reported. Clinicians caring for children should remain vigilant for this rare complication of influenza B virus infection.

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