Influenza A–Associated Encephalopathy with Bilateral Thalamic Necrosis in Japan

Two cases of acute encephalopathy in young children clearly showed evidence of influenza A virus infection and bilateral thalamic lesions. Influenza-associated encephalopathy with bilateral thalamic lesions has mostly been reported in Japan; it differs from Reye’s syndrome in several respects. Other factors in addition to influenza virus infection may have contributed to the etiology of encephalopathy in our case patients.

It is estimated that >100 children die of influenza-associated encephalopathy (influenza encephalopathy) in Japan every year; these cases are typically associated with sudden onset of high-grade fever, severe convulsions, rapidly progressive coma, and death within 2 or 3 days [1–5]. Cases of influenza encephalopathy in Japan resemble acute cases of influenza A virus–associated encephalopathy reported by Delorme et al. [6], rather than cases of Reye’s syndrome or postinfluenza encephalopathy seen during an influenza epidemic [7]. There are clinical distinctions between influenza encephalopathy and Reye’s syndrome. In influenza encephalopathy, there is no history of taking aspirin; there is rapid loss of consciousness, with coma ensuing within 24 h; convulsions occur in almost all patients in the early stage of onset; and hyperammonemia is rarely seen. Moreover, neuroimaging of patients with influenza encephalopathy often reveals bilateral thalamic lesions, which have not been demonstrated in cases of Reye’s syndrome. In the winter season of 1998–1999, we encountered 2 fatal cases of typical influenza A encephalopathy with characteristic brain lesions.

A 3-year-old girl (case patient 1) became ill with a cough on 12 January 1999; she had a high-grade fever develop on 13 January. On 14 January, she was treated with cefdinir (antimicrobial),
procaterol (β₂-adrenergic agent), ambroxol (expectorant), alimemadine (antihistamine), and acetaminophen. That evening, she had generalized seizures and was treated with a diazepam suppository. The patient’s condition improved, and she was released; however, on 15 January, she was admitted again because of stupor. Results of laboratory tests revealed abnormal liver function (aspartate aminotransferase level, 295 U/L; alanine aminotransferase level, 136 U/L) and abnormal coagulation. Serum level of ammonia was normal. Analysis of CSF obtained by lumbar puncture revealed a normal cell count (0 cells/mm³), and brain CT at the time of admission was normal. The clinical diagnosis was acute encephalopathy.

Despite treatment with glycerol, acyclovir, and dexamethasone, the patient became comatose and had respiratory arrest on the same day (15 January). She subsequently died on 31 January. Brain CT done on 17 January revealed bilateral thalamic hemorrhage and peripheral low density (figure 1, top). Influenza A (H3N2) virus was isolated from a throat-swab specimen obtained on 18 January. Serum hemagglutination inhibition (HI) titers of A/Sydney/5/97 (H3N2) virus increased from <1:8 on 18 January to 1:256 on 22 January. She had not received influenza vaccine for this season.

A 1-year-old boy (case patient 2) had a high-grade fever followed by vomiting develop on 16 January 1999. After having generalized seizures, he was brought to our hospital, was treated with a diazepam suppository, and was released. His prescribed medications were erythromycin, tulobuterol (β₂-adrenergic agent), ambroxol, carbocisteine (expectorant), bromhexine (expectorant), and ephedrine. On 17 January, he was admitted to our hospital because he failed to respond to his mother’s call and subsequently became comatose. Results of laboratory tests revealed abnormal liver function (aspartate aminotransferase level, 573 U/L; alanine aminotransferase level, 379 U/L) and abnormal coagulation. Serum levels of ammonia and C-reactive protein were normal. Analysis of CSF obtained by lumbar puncture showed a normal cell count (1 cell/mm³), although a brain CT revealed bilateral thalamic low density (figure 1, bottom). The clinical diagnosis was acute encephalopathy.

The patient never regained consciousness and died on 17 February. Influenza A (H3N2) virus was isolated from a throat-swab specimen obtained on 18 January. Serum HI titers of A/Sydney/5/97 (H3N2) virus increased from <1:8 on 18 January to 1:128 on 2 February. Virus isolation and reverse transcription–PCR analysis did not detect virus in CSF. The patient had not received influenza vaccine for this season.

We report 2 cases of acute encephalopathy that clearly showed evidence of influenza A virus infection: the virus was isolated, HI titers were elevated, and neuroimaging revealed bilateral thalamic lesions in both case patients. Acute encephalopathy with bilateral thalamic lesions, designated as “acute necrotizing encephalopathy” (ANE), has mostly been reported in Japan [8]. At least 10%–20% of recent cases of influenza encephalopathy in Japan have been diagnosed as ANE on the basis of CT findings [1–5]. In addition to influenza A, characteristic thalamic lesions have been associated with other viral infections, such as influenza B and exanthema subitum [8]. Approximately 20% of these cases have been associated with influenza A. For this reason, the etiology of ANE cannot be attributed to a specific viral infection, which suggests that some other factors in addition to influenza virus infection may have contributed to the etiology of encephalopathy in our case patients. The neuropathology of ANE consists of petechial hemorrhages and congestion of intraparenchymatous thalamic vessels, with necrosis of surrounding tissue [8]. Therefore, ANE may be caused by some vasoactive substance or by a process leading to vasoconstriction in CNS.

According to a recent report, influenza virus has only infrequently been detected by reverse transcription–PCR analysis of CSF specimens from patients with influenza encephalopathy, which suggests that influenza encephalopathy may not be
caused by direct viral invasion of the CNS [9]. Indeed, many issues need to be clarified regarding the association between the pathogenesis of encephalopathy and influenza virus infection. We must, therefore, further investigate the factors contributing to influenza encephalopathy, including viral factors (such as protein variability, as reported elsewhere [10]), effects of such cytokines as IL-6 and TNF-α (the levels of which increase in patients with encephalopathy [5,9]), and medications (especially vasoactive drugs) that are frequently used in Japan but not in Western countries and that are prescribed before the onset of neurological symptoms.

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References

Bacteremic Pneumonia Due to Multidrug-Resistant Pneumococci in 3 Patients Treated Unsuccessfully with Azithromycin and Successfully with Levofloxacin

Three patients with bacteremic pneumonia caused by multidrug-resistant Streptococcus pneumoniae were treated unsuccessfully with azithromycin. One S. pneumoniae isolate carried a mef determinant for an efflux pump; a second isolate had an erm determinant. All 3 patients were successfully treated with levofloxacin, an antipneumococcal fluoroquinolone.

Lower respiratory tract infections with penicillin-resistant Streptococcus pneumoniae are a growing concern. These infections are often treated empirically with agents such as macrolides, cephalosporins, or trimethoprim-sulfamethoxazole when in vitro testing may indicate nonsusceptibility. Isolates resistant to penicillin are also increasingly resistant to other antimicrobial classes such as the macrolides and the antifolates [1,2]. In vitro testing may indicate nonsusceptibility. Isolates resistant to penicillin are also increasingly resistant to other antimicrobials such as the macrolides and the antifolates [1,2]. In a multicenter surveillance study conducted during the 1997–1998 respiratory illness season in the United States, 13% of 4148 pneumococcal isolates were resistant to penicillin, and 21%–22% were resistant to macrolides [1]. To date, reports of infection treatment failures caused by multidrug-resistant S. pneumoniae have been rare, in part because of the frequent use of empirical therapy in the absence of data from antibiotic susceptibility testing. However, there have been a limited number of literature reports of isolated infections caused by these organisms that have not responded to therapy with a β-lactam or macrolide agent [3–5]. In some cases, patients were colonized by a resistant organism after treatment with a macrolide [4], whereas in other cases treatment failures were reported [3–5]. In this report, we describe 3 bacteremic patients infected with penicillin- and macrolide-nonsusceptible S. pneumoniae.

From November 1996 to September 1997, 3 patients presented at Spartanburg Regional Medical Center (Spartanburg, SC) with bacteremic community-acquired lower respiratory tract infection from drug-resistant S. pneumoniae after 3–5 days of therapy with 250 mg of azithromycin (loading dose, 500 mg) (table 1). Each patient responded to empirical treatment with levofloxacin (500 mg daily); there was complete resolution of symptoms and chest roentgenogram abnormalities after 14 days of oral therapy.

The first patient was a healthy nonsmoking 44-year-old woman who received azithromycin therapy for cough, chills, and fever (temperature, 39.4°C). On day 5, she presented to the emergency department with fever (temperature, 39.9°C) and an extensive left lower lobe and lingular infiltrate diagnosed by chest roentgenography. Analysis of bronchial washings showed polymorphonuclear leukocytes and gram-positive diplococci.