Encephalopathy Associated with Influenza B in a Healthy Young Man

Masaki Shimamoto¹, Satoshi Okada² and Takeshi Terashima³

Abstract

A 19-year-old man presented with a fever, convulsions, and loss of consciousness at our hospital. The patient had a Glasgow Coma Scale score of 12. Influenza B virus infection was diagnosed using the rapid test kit, and an eight-fold increase in the serum levels of anti-influenza B virus antibody was confirmed using the complement fixation test. Brain magnetic resonance imaging showed multifocal high-signal lesions, and an electroencephalogram showed diffuse slowing of the background activity, indicating acute encephalopathy. After treatment with peramivir and methylprednisolone for 3 days, the patient was discharged without any neurological impairment. This was a case of influenza B infection associated with acute encephalopathy in a healthy young man.

Key words: influenza B, encephalopathy, adult, methylprednisolone

(Intern Med 56: 1925-1929, 2017)

DOI: 10.2169/internalmedicine.56.8170

Introduction

Influenza virus infections are associated with various neurological complications, the most common of which are seizures and encephalopathy. Encephalopathy is most frequently reported in children. Although the number of reported cases in adults has been increasing recently, the majority have been associated with influenza A (H3N2) (1, 2). While the emergence of influenza A (H1N1) is correlated with increased reports of neurological manifestations (3), there have been a few cases of influenza B-associated encephalopathy in adults (4). In this report, we describe the detailed clinical course of influenza B infection associated with acute encephalopathy in a healthy young man. Our discussion includes details of the brain magnetic resonance imaging (MRI) and electroencephalogram (EEG) findings.

Case Report

A 19-year-old man was transferred to our emergency department after the onset of convulsions and loss of consciousness in March 2016. The patient had a medical history of febrile seizures in childhood. He had not received influenza vaccination during the season. Initially, the patient’s body temperature had risen to 38.5°C at home, and he had presented with convulsions and loss of consciousness 7 hours following the onset of a fever. The patient did not have a cough, nasal discharge, sore throat, headache, arthralgia, or sore muscles. In the emergency room, he appeared to be a well-developed, well-nourished man. His body temperature was 39.1°C, blood pressure was 139/68 mmHg, pulse was 96 beats/min, respiratory rate was 21 breaths/min, and oxygen saturation was 97% on room air. The Glasgow Coma Scale (GCS) score was 4 for eye opening (E), 4 for best verbal response (V), and 6 for best motor response (M). The physical examination was unremarkable, and his pupillary reflexes were normal. Neck rigidity and Kernig’s sign were not apparent. He had a generalized convolution lasting 1 minute in the emergency room.

The nasopharyngeal swab sample was analyzed using a rapid test kit (Quick Chaser Flu A, B; Mizuho Medy, Japan) and did not indicate the presence of either influenza A or B viral antigen. An initial laboratory examination showed a white blood cell count of 4,500/μL (62% neutrophils), C-reactive protein level of 1.46 mg/dL, blood urea nitrogen

1Department of Internal Medicine, Tokyo Dental College Ichikawa General Hospital, Japan, 2Department of Neurology, Tokyo Dental College Ichikawa General Hospital, Japan and 3Department of Respiratory Medicine, Tokyo Dental College Ichikawa General Hospital, Japan

Received for publication August 23, 2016; Accepted for publication December 12, 2016

Correspondence to Dr. Takeshi Terashima, terasima@tdc.ac.jp
level of 8.8 mg/dL, and creatinine level of 1.06 mg/dL. The serum interleukin (IL)-6 level was 9.06 pg/mL (normal range, <2.41 pg/mL). Lumbar puncture was performed, and a cerebrospinal fluid analysis revealed a normal cell count (<1/μL), a protein level of 27.9 mg/dL, and a glucose level of 94 mg/dL. A computed tomography (CT) scan of the brain and chest radiograph showed normal findings. The anti-influenza virus treatment peramivir was started based on the information that there had been an outbreak of influenza A and B virus infections in the area during that time.

After admission, the patient’s consciousness level worsened. He was somnolent with closed eyes. The GCS score was 12 (E2V4M6). Brain T2- and diffusion-weighted MRI on the same day showed multifocal high-signal lesions in the right parietal and frontal lobes, indicating acute encephalopathy (Fig. 1). On day 2 following admission, a repeated examination of a nasopharyngeal swab sample indicated the presence of influenza B virus antigen. The patient was treated with peramivir (300 mg/day) and methylprednisolone (1,000 mg/day) for 3 days. An EEG on day 5 showed diffuse slowing of the background activity consistent with encephalopathy (Fig. 2). The patient’s physical condition gradually improved (Fig. 3). The serum IL-6 level was decreased to 0.673 pg/mL on day 8. The patient was discharged without any neurological impairment on day 10 and has been followed up at an outpatient clinic. An examination showed no evidence of underlying diseases or immunodeficiency. His serum levels of immunoglobulin G, A, and M were normal. Brain MRI and EEG on day 20 following the onset showed no abnormal findings. In addition, the serum antibody titers against influenza B virus, as measured using the complement fixation test, were 1:8 on admission and 1:64 on day 20. The serum antibody titer against influenza A virus was not found to be increased at admission or throughout the clinical course.
Discussion

In this report, we describe a case of encephalopathy associated with influenza B virus infection in a previously healthy young man. To our knowledge, there have only been a few reported cases of acute encephalopathy associated with influenza B virus infection in an adult (4, 5). The diagnosis of influenza-associated encephalopathy requires the definitive diagnosis of an influenza virus infection and acute onset of encephalopathy, according to the diagnostic criteria of the Japanese research committee of influenza encephalopathy (6). The criteria for acute encephalopathy include severe impairment of consciousness on admission, with a GCS score of ≤10-11 or documented brain CT findings, or a sustained GCS score of ≤13 for more than 24 hours. In this case, an influenza B virus infection was diagnosed based on the rapid test kit, which confirmed an 8-fold increase in the serum levels of anti-influenza B virus antibody. Encephalopathy was diagnosed based on the sustained impaired consciousness level (GCS score of 12) and was supported by the brain MRI and EEG findings.

Goenka et al. (5) proposed the categorization of neurological manifestations of influenza, and the categories were subsequently developed by Akins et al. (3). This categorization is based on the increasing presence of neurological sequelae and mortality. The mildest is febrile seizures, followed by acute movement disorder, acute benign encephalopathy/encephalitis, and acute encephalopathy syndromes. Acute encephalopathy syndromes include mild encephalitis/encephalopathy with a reversible splenial lesion (MERS), acute necrotizing encephalopathy (ANE), acute encephalopathy with biphasic seizures and late reduced diffusion (AEDS), acute infantile encephalopathy predominantly affecting the frontal lobes, acute shock with encephalopathy and multiorgan failure, and acute hemorrhagic leuko-
The pathogenesis of influenza-associated encephalopathy remains unclear. A hyperactive cytokine response, rather than viral invasion, is believed to be responsible (1, 7). We found a high serum concentration of IL-6 in our patient. It was reported that the level of IL-6 is related to the disease severity and the duration of unconsciousness in patients with influenza-associated encephalopathy (8, 9).

Considering that the immunogenic consequence of influenza virus infection likely contributes to the pathogenesis, steroid pulse therapy is recommended as a specific therapy for influenza-associated encephalopathy (10). Indeed, our case showed dramatic improvement in consciousness following steroid therapy. Previous case reports have reported improvements in severe cases of encephalopathy following the use of corticosteroids (11). Conversely, Kawashima et al. (12), who surveyed medical doctors who had treated pediatric influenza-associated encephalopathy, showed that the administration of corticosteroids did not affect the treatment results. Therefore, a well-designed, randomized, controlled study to evaluate the effect of corticosteroid administration on influenza-associated encephalopathy is needed.

Influenza-associated encephalopathy is most frequently reported in children. Among the 25 cases from the British survey reported by Goenka et al. (5), 21 were children, and 4 were adults. Two of the adults had acute benign encephalopathy associated with influenza A (H1N1). There was a report of two cases of influenza B-associated encephalopathy in adults; they were virologically documented, with normal MRI findings and EEG findings consistent with encephalitis (4). In Japan, influenza is the most commonly identified pathogen in acute encephalopathy and is detectable by rapid detection kits for influenza infection, which are widely used among physicians. Influenza-associated encephalopathy is widely recognized in Japan, where its incidence has been estimated as 100-500 cases per year (6). The majority of patients are infants or young children aged <5 years. Table shows the number of influenza B-associated encephalitis/encephalopathy cases that were reported during the influenza seasons from 2007 to 2016 in Japan (13, 14). According to information from the National Institute of Infectious Diseases, Japan, epidemics of influenza B occurred during the winters of 2010-2011, 2011-2012, 2013-2014, and 2015-2016 (15). Table shows that the number of cases of influenza B-associated encephalitis was high in the seasons when an epidemic of influenza B occurred.

This case report showed the detailed clinical course of encephalopathy associated with influenza B infection in an adult. The MRI and EEG findings in the acute phase were consistent with encephalopathy and returned to normal in the recovery phase. During outbreaks of influenza A and B, we suggest that physicians consider the possibility of influenza-associated encephalopathy and initiate therapy im-

| Age (years) | 2007-2010 | 2010-2011 | 2011-2012 | 2012-2013 | 2013-2014 | 2014-2015 | 2015-2016 | Season | Total |
|-------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|--------|-------|
| 0-4         | 7         | 4         | 7         | 2         | 8         | 0         | 22        | 50     |
| 5-9         | 6         | 9         | 9         | 3         | 7         | 1         | 16        | 51     |
| 10-19       | 2         | 1         | 8         | 3         | 9         | 0         | 13        | 36     |
| 20-29       | 0         | 1         | 0         | 1         | 0         | 0         | 1         | 2      |
| 30-39       | 0         | 0         | 2         | 0         | 0         | 0         | 2         | 4      |
| 40-49       | 0         | 0         | 0         | 2         | 0         | 0         | 6         | 8      |
| 50-59       | 1         | 0         | 1         | 0         | 0         | 1         | 1         | 4      |
| 60-69       | 0         | 0         | 0         | 0         | 3         | 1         | 2         | 6      |
| 70-79       | 0         | 0         | 0         | 1         | 0         | 0         | 1         | 2      |
| ≥80         | 0         | 0         | 0         | 0         | 2         | 2         | 1         | 5      |
| Total       | 16        | 15        | 27        | 10        | 31        | 5         | 64        | 168    |
media-tely for adults and children presenting with a fever and impaired consciousness.

The authors state that they have no Conflict of Interest (COI).

References

1. Morishima T, Togashi T, Yokota S, et al; Collaborative Study Group on Influenza-Associated Encephalopathy in Japan. Encephalitis and encephalopathy associated with an influenza epidemic in Japan. Clin Infect Dis 35: 512-517, 2002.
2. Sugaya N. Influenza-associated encephalopathy in Japan. Semin Pediatr Infect Dis 13: 79-84, 2002.
3. Akins PT, Belko J, Uyeki TM, Axelrod Y, Lee KK, Silverthorn J. H1N1 encephalitis with malignant edema and review of neurologic complications from influenza. Neurocrit Care 13: 396-406, 2010.
4. Ak Ö, Biteker F, Cag Y, et al. Influenza B-associated encephalopathy in two adults. J Infect Chemother 18: 961-964, 2012.
5. Goenka A, Michael BD, Ledger E, et al. Neurological manifestations of influenza infection in children and adults: results of a National British Surveillance Study. Clin Infect Dis 58: 775-784, 2014.
6. Mizuguchi M. Influenza encephalopathy and related neuropsychiatric syndromes. Influenza Other Respir Viruses 7 (Suppl 3): 67-71, 2013.
7. Kawada J, Kimura H, Ito Y, et al. Systemic cytokine responses in patients with influenza-associated encephalopathy. J Infect Dis 188: 690-698, 2003.
8. Nakamura M, Yamanaka G, Kawashima H, et al. Clinical application of rapid assay of interleukin-6 in influenza-associated encephalopathy. Dis Markers 21: 199-202, 2005.
9. Aiba H, Mochizuki M, Kimura M, Hojo H. Predictive value of serum interleukin-6 level in influenza virus-associated encephalopathy. Neurology 57: 295-299, 2001.
10. Morishima T, Okabe N, Namakura Y, et al. Guideline for influenza encephalopathy: revised edition. Jpn J Pediatr 62: 2483-2528, 2009 (in Japanese).
11. Kawashima H, Togashi T, Yamanaka G, et al. Efficacy of plasma exchange and methylprednisolone pulse therapy on influenza-associated encephalopathy. J Infect 51: E53-E56, 2005.
12. Kawashima H, Morichi S, Okumara A, Nakagawa S, Morishima T; Collaborative Study Group on Influenza-Associated Encephalopathy in Japan. Treatment of pandemic influenza A (H1N1) 2009-associated encephalopathy in children. Scand J Infect Dis 44: 941-947, 2012.
13. The National Institute of Infectious Diseases (NIID). Pandemic influenza A (H1N1) 2009-associated encephalopathy and encephalitis. Infectious Diseases Weekly Report (IDWR) 2010 41: 14-20, 2010.
14. The National Institute of Infectious Diseases (NIID). Infectious Diseases Weekly Report (IDWR). [cited 2016 Jul 9]. Available from: http://www.nih.go.jp/niid/ja/idwr-dl.html
15. The National Institute of Infectious Diseases (NIID). Infectious Agents Surveillance Report. Monthly reports of virus isolation/detection from human sources. [cited 2016 Nov 6]. Available from: http://www.nih.go.jp/niid/ja/diseases/flu.html

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).