

Case Report

Influenza A (H1N1)-associated severe complications; hemolytic uremic syndrome, myocarditis, acute necrotizing encephalopathy

Sevliya Öcal Demir¹, Serkan Atıcı¹, Eda Kepenekli Kadayıfci¹, Gülşen Akkoç¹, Nurhayat Yakut¹, Feyza İnceköy Girgin², Nilüfer Yalındağ Öztürk², Ahmet Soysal¹

¹ Department of Pediatrics, Division of Pediatric Infection Disease, Marmara University School of Medicine, Istanbul, Turkey

² Department of Pediatrics, Pediatric Intensive Care Unit, Marmara University School of Medicine, Istanbul, Turkey

Abstract

Influenza is a generally self-limited infection agent that only rarely causes severe complications. To increase awareness about its serious complications, we report three cases of influenza A (H1N1) infection complicated with hemolytic uremic syndrome, myocarditis and acute necrotizing encephalopathy. In all three cases, nasopharyngeal samples confirmed influenza A (H1N1) infection by antigen test and multiplex PCR detection. The first case, a 3-year-old girl, had respiratory distress, anemia, thrombocytopenia and renal failure at admission, and was diagnosed with hemolytic uremic syndrome. Supportive treatment and oseltamivir did not prevent the development of chronic renal failure. The second case, a 5-year-old girl admitted with lethargia and flu-like symptoms and was diagnosed with myocarditis and cardiogenic shock. Oseltamivir and supportive treatment including extra-corporeal membrane oxygenation (ECMO) failed. She died on the 3rd day of admission. The third case, a 21-month-old boy, presented with decreased level of consciousness and was diagnosed with acute necrotizing encephalopathy with the aid of cranial magnetic resonance imaging (MRI). He was discharged without any neurological sequelae three weeks after admission. It should be kept in mind that influenza virus does not always cause a self-limited flu. Multidisciplinary management, early diagnosis and antiviral treatment are critical for the disease and to prevent its life-threatening complications.

Key words: influenza; H1N1; complications; encephalopathy; HUS; myocarditis.

J Infect Dev Ctries 2019; 13(1):83-86. doi:10.3855/jidc.10049

(Received 12 December 2017 – Accepted 16 August 2018)

Copyright © 2019 Öcal Demir *et al.* This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Influenza is a virus that usually causes acute self-limited respiratory illness. About 20% of children worldwide develop symptomatic influenza A or B infections each year [1]. Its most common complications are pneumonia, secondary bacterial infections and sepsis. Although influenza is mainly considered an infection limited to the respiratory tract, clinical reports demonstrate that it also involves other organ systems [2]. Influenza A (H1N1)-associated extrapulmonary complications including myositis, rhabdomyolysis, renal insufficiency, hemolytic uremic syndrome (HUS), myocarditis, pericarditis, encephalopathy, encephalitis, Guillain-Barré syndrome, aseptic meningitis, transverse myelitis were reported. Of them the most frequently described clinical diseases were viral myocarditis and viral encephalitis [2].

Here we present cases of three previously healthy children admitted with severe influenza A (H1N1) complications in January 2016. Our aim was to draw attention to serious complications of H1N1, to enable

early diagnosis, appropriate treatment and improve prognosis.

Case Reports

Case 1

A 3-year-old girl was admitted to the pediatric intensive care unit (PICU) with respiratory distress. Her blood pressure, body temperature, pulse and respiratory rate were 188/104 mmHg, 37.8 °C, 110/minute and 38/minute, respectively. On physical examination, dyspnea, decreased breath sound and rales on lower zone of both lungs, hepatosplenomegaly were noted. Laboratory tests showed anemia (hemoglobin:6.1 gr/dL), thrombocytopenia (76000mm³/ml), hemolysis, reticulocytosis (11%) and high creatinine level (4.75 mg/dL). Pleural effusion and renal parenchymal disease were detected on radiological imaging. Antigen test and multiplex polymerase chain reaction (PCR) revealed influenza A (H1N1) in the nasopharyngeal sample. Latex agglutination test and multiplex PCR were negative for *Escherichia coli* O157 H7 in the stool sample. The patient was diagnosed with acute renal

failure, secondary to hemolytic uremic syndrome associated with the influenza A (H1N1) virus. Oseltamivir treatment was administered for 5 days. She needed mechanical ventilation for 18 days, on the 27th day of admission she was transferred to general ward and discharged after a couple of days. She is still on peritoneal dialysis program.

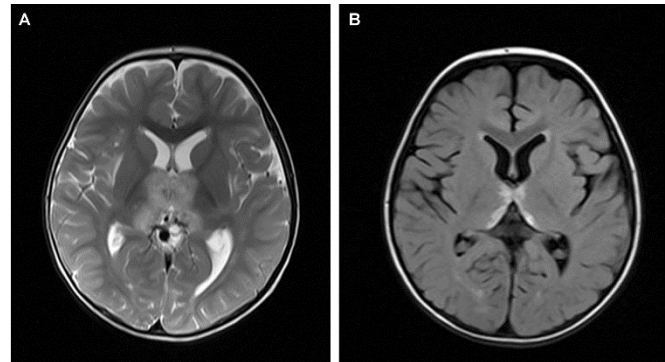
Case 2

A 5-year-old girl presented with flu-like symptoms, diarrhea, vomiting and abdominal pain. On physical examination she was lethargic, hypotensive (blood pressure: 77/42 mmHg), tachycardic (pulse: 168/minute), tachypneic (respiratory rate: 36/minute) and febrile (body temperature: 38°C). Examination of the lungs showed a few coarse crackles in lungs and blood gas analysis revealed pH 7.24, pCO₂: 59 mmHg, HCO₃: 21 mm/L, base excess: 3.5 mmol/L, lactate: 4.1 mmol/L. Cardiac enzymes were elevated (CK: 2665U/L, mass CK-MB: 125 ng/mL, cardiac troponin I: 2.17 ng/mL), chest radiography was normal. Echocardiography (ECO) revealed acute heart failure with low ejection fraction (24%) and minimal pericardial effusion. The supportive treatment including intravenous fluid and inotropes was initiated. The patient was admitted to the PICU with the diagnosis of myocarditis and cardiogenic shock and she was intubated. Cardiogenic shock was resistant to all medical treatments, extra-corporeal membrane oxygenation (ECMO) was planned. She had cardiac arrest during the catheterization and turned to life after 40 minutes resuscitation. When she was a bit stabilized, the catheter was inserted and ECMO was started. Influenza A (H1N1) antigen and PCR tests were reported as positive in nasopharyngeal aspirate sample and oseltamivir treatment was initiated. Unfortunately, she died on the 3rd day of PICU admission despite the ECMO and the antiviral treatment.

Case 3

A 21-month-old boy presented with flu-like symptoms, fever and decreased level of consciousness. He responded to painful stimuli with flexion and meaningless sounds, his Glasgow Coma Scale (GCS) was 7. The blood parameters were normal (leukocyte count: 8300 /mm³, C-reactive protein: < 3.3 mg/L). Cerebrospinal fluid (CSF) examination showed, glucose: 57 mg/dL, protein: 104.8 mg/dL and 1 cell/mm³ on the smear. Enterovirus and herpesvirus PCR tests were negative in the CSF. Influenza A (H1N1) antigen and multiplex PCR tests were positive in the nasopharyngeal samples, but not in the CSF.

Figure 1. MRI of the third case's brain A) On admission it demonstrates hyperintense lesions in the bilateral mammillary bodies, thalami, meziotemporal region, external capsule on T2 weighted imaging; B) After oseltamovir treatment for 3 weeks it demonstrates hyperintense lesions in the in medial of thalami and external capsule healed as a residual.



Oseltamivir treatment was initiated. Magnetic resonance imaging (MRI) of the brain demonstrated hyperintense lesions in the bilateral mammillary bodies, thalami, meziotemporal region, external capsule and in the left anterior half of the medulla oblongata on T2 weighted imaging (Figure 1A). These findings were consistent with acute necrotizing encephalitis (ANE). His EEG was normal. On the second day of antiviral therapy, GCS turned to 15. He was transferred to a general ward and oseltamivir treatment was continued for three weeks until the lesions healed as a residual in the follow-up brain MRI (Figure 1B). The patient was discharged without neurological sequelae.

The same microbiological methods were performed in all 3 cases for influenza A (H1N1) diagnosis. We evaluated the clinical nasopharyngeal samples of the 3 patients using SD Bioline Influenza Antigen Test kit (Abbott, USA) to detect the influenza virus. The Xpert Flu Assay (Cepheid, Sunnyvale, USA) technology was used for H1N1 identification. This method is a next-generation nucleic acid amplification system that provides multiplexed PCR detection of the influenza A (H1N1) [3].

Discussion

Influenza can unexpectedly be associated with severe morbidity and mortality especially in children who are under the age of four, taking aspirin treatment and have chronic underlying disease or immunodeficiency. However, severe complications of influenza can also develop in healthy children as in these 3 cases. In the 2016-2017 influenza season, more than 40% of all hospitalized children had not known underlying conditions. [4].

The first case with atypical HUS had preceding flu-like symptoms with fever and was influenza A (H1N1) positive in her nasopharyngeal aspirate. Influenza A H1N1 has been reported as a trigger in many cases of atypical HUS as in our first case [5-7]. Although the trigger mechanism is unknown, some authors have suggested that the viral neuraminidase protein unmasks the Thomsen-Friedenreich cryptoantigen, which has previously been implicated in atypical HUS [8,9]. Early onset antiviral treatment is related to improved prognosis for children with severe disease or complications. Therefore when indicated, antiviral treatment should be initiated immediately after the diagnosis, ideally within 48 hours [10]. Unfortunately, here for the patient diagnosed with HUS oseltamivir was initiated one week after symptoms developed and was given for only 5 days. Oseltamivir should be started earlier and given for a prolonged duration in severe illness [11,12]. Its regimens have been well-tolerated as long as 42 days [13].

The second patient was diagnosed with influenza A (H1N1)-associated fulminant myocarditis. Although endomyocardial biopsy is the gold standard for diagnosis, it is invasive, vulnerable to sampling errors, and has limited sensitivity [14]. For these reasons, diagnosis is made with imaging techniques like ECO, MRI and coronary angiography in addition to clinical findings. In our patient, H1N1-associated myocarditis was diagnosed with clinical findings (sudden cardiac insufficiency), elevation of cardiac enzymes, ECO findings (reduced ejection fraction) and detection of influenza A virus in the nasopharyngeal aspirate. H1N1-associated fulminant myocarditis has a high mortality rate despite intensive care. Ukimura *et al.* reviewed the data of 58 patients (28 males and 30 females; mean age 32 years) with H1N1-associated myocarditis worldwide and determined a mortality rate of 24% [15]. On the other hand, Saji *et al.* reported a mortality rate of 83% in patients who do not respond to initial medical treatment and do not receive mechanical circulation support [16]. In this group extracorporeal membrane oxygenation (ECMO) can reduce mortality rate to less than 20% [17]. Treatment failure in our patient may be due to the severity of her myocarditis. She had cardiac arrest before ECMO, was resuscitated about 40 minutes and developed multiorgan failure probably because of hypoxia. Patients recovering from acute fulminant myocarditis, although severely ill, may be more likely to fully recover if they survive the acute phase of the disease. Therefore, adequate hemodynamic support is very important in the acute phase of major cardiac instability [18].

The third case was diagnosed with influenza A (H1N1)-associated acute encephalopathy which is an uncommon, severe complication that can result in high neurological sequelae or mortality especially in children [19]. Pathogenesis is not clearly known; viral invasion of the central nervous system (CNS), damage of proinflammatory cytokines, metabolic disorders and genetic predisposition are blamed [20]. Whether the influenza virus invade the CNS or not is not clear. In our patient, influenza A (H1N1) antigen and multiplex PCR tests were negative in CSF. Fujimoto *et al.* reported that influenza virus RNA was commonly positive in CSF of patients who developed ANE [21], whereas other reports detected only a small number of patients who were positive for viral RNA in CSF and brain. In addition, there was a lack of inflammation in brain tissue of fatal cases [22-25]. Influenza encephalitis is usually seen in the early phase of infection, with the majority of patients being children younger than 5 years (78-82%) [26]. Our case was 21 months old, his conscious level decreased on the 3rd day of symptoms. Antiviral treatment was initiated on the 2nd day of admission. The most severe form of H1N1-associated encephalitis is acute necrotizing encephalopathy. Neurologic sequelae are seen in 20-28% and the mortality rate is 27-37% [27]. In severe necrotizing encephalitis, multifocal symmetrically distributed lesions are present in the thalamus, cerebral white matter, brain stem, cerebellum and parenchyma on CT or MRI. EEG can show widespread slowing, frontal and temporal focal slowing, and sharp waves without epileptic activity. In our case findings of MRI were compatible with acute necrotizing encephalitis and EEG was normal. Since there was no accurate data about the duration of antiviral therapy for H1N1-associated encephalopathy, oseltamivir treatment was continued until the lesions resolved as a residual on follow-up brain MRI. No side effects were observed, and the patient was discharged without sequelae.

Conclusion

Physicians should keep in mind that the flu caused by the influenza virus might not always be self-limited. Multidisciplinary management, early diagnosis and antiviral treatment are critical for the disease and to prevent its life-threatening complications. Severe complications should be suspected from influenza in severely ill children in influenza season. Clinical findings should be assessed in detail, laboratory tests performed rapidly and the antiviral treatment administered as early as possible.

References

1. The Lancet Neurology (2009) Pandemic influenza: a priority for the neurological community, *The Lancet Neurology* 8: 869.
2. Sellers SA, Hagan RS, Hayden FG, Fischer WA 2nd (2017) The hidden burden of influenza: A review of the extra-pulmonary complications of influenza infection. *Influenza Other Respir Viruses* 11: 372-393.
3. Novak-Weekley SM, Marlowe EM, Poulter M, Dwyer D, Speers D, Rawlinson W, Baleriola C, Robinson CC (2012) Evaluation of the Cepheid Xpert Flu Assay for rapid identification and differentiation of influenza A, influenza A 2009 H1N1, and influenza B viruses. *J Clin Microbiol* 50: 1704-1710.
4. American Academy of Pediatrics (2018) Influenza. In Kimberlin DW, Brady MT, Jackson MA, Long SS, editors *Red Book: 2018 Report of the Committee on Infectious Diseases*, 31th edition. Itasca, IL: 476-490.
5. Asaka M, Ishikawa I, Nakazawa T, Tomosugi N, Yuri T, Suzuki K (2000) Hemolytic uremic syndrome associated with influenza A virus infection in an adult renal allograft recipient: Case report and review of the literature. *Nephron* 84: 258–266.
6. Watanabe T (2001) Hemolytic uremic syndrome associated with influenza A virus infection. *Nephron* 89: 359–360.
7. Bento D, Mapril J, Rocha C, Marchbank KJ, Kavanagh D, Barge D, Strain L, Goodship THJ, Meneses-Oliveira C (2010) Triggering of atypical uremic syndrome by influenza A(H1N1). *Ren Fail* 32: 753-756.
8. Beebe DP, Schreiber RD, Cooper NR (1983) Neutralization of influenza virus by normal human sera: Mechanisms involving antibody and complement. *J Immunol* 130: 1317-1322.
9. Rhee H, Song SH, Lee YJ, Choi HJ, Ahn JH, Seong EY, Lee SB, Kwak IS (2011) Pandemic H1N1 influenza A viral infection complicated by atypical hemolytic uremic syndrome and diffuse alveolar hemorrhage. *Clin Exp Nephrol* 15: 948-952.
10. Centers for Disease Control and Prevention (2018) Influenza antiviral medications: Summary for clinicians. Available: <https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm>. Accessed: 03 December 2018).
11. Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM; Centers for Disease Control and Prevention (CDC) (2011) Antiviral agents for the treatment and chemoprophylaxis of influenza - recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 60: 1-24.
12. Munoz FM (2018) Seasonal influenza in children: Prevention and treatment with antiviral drugs: An overview. Mallory GB, Edwards MS editors. UpToDate; Last updated 9.4.2018. Available: www.uptodate.com/contents/seasonal-influenza-in-children-prevention-and-treatment-with-antiviral-drugs. Accessed 31 December 2018.
13. Khazeni N, Bravata DM, Holty JE, Uyeki TM, Stave CD, Gould MK (2009) Systematic review: safety and efficacy of extended-duration antiviral chemoprophylaxis against pandemic and seasonal influenza. *Ann Intern Med* 151: 464-473.
14. Baughman KL (2006) Diagnosis of myocarditis: death of Dallas criteria. *Circulation*. 113: 593-595.
15. Ukimura A, Izumi T, Matsumori A (2010) Clinical Research Committee on Myocarditis Associated with 2009 Influenza A (H1N1) Pandemic in Japan organized by Japanese Circulation Society. A national survey on myocarditis associated with 2009 Influenza A (H1N1) Pandemic in Japan. *Circ J* 74: 2193-2199.
16. Saji T, Matsuura H, Hasegawa K, Nishikawa T, Yamamoto E, Ohki H, Yasukochi S, Arakaki Y, Joo K, Nakazawa M (2012) Comparison of the clinical presentation, treatment, and outcome of fulminant and acute myocarditis in children. *Circ J* 76: 1222-1228.
17. Bohn D, Macrae D, Chang AC (2006) Acute viral myocarditis: mechanical circulatory support. *Pediatr Crit Care Med* 7: 21-24.
18. Schultz JC, Hilliard AA, Cooper LT Jr, Rihal CS (2009) Diagnosis and treatment of viral myocarditis. *Mayo Clin Proc Nov*; 84 : 1001-1009.
19. Kasai T, Togashi T, Morishima T (2000) Encephalopathy associated with influenza epidemics. *Lancet* 355: 1558-1559.
20. Wang GF, Li W, Li K (2010) Acute encephalopathy and encephalitis caused by influenza virus infection. *Curr Opin Neurol* 23: 305-311.
21. Fujimato S, Kobayasi M, Uemura O, Iwasa M, Ando T, Katoh T, Nakamura C, Maki N, Togari H, Wada Y (1998) PCR on cerebrospinal fluid to show influenza-associated acute encephalopathy or encephalitis. *Lancet* 352: 873-875.
22. Togashi T1, Matsuzono Y, Narita M, Morishima T (2004) Influenza-associated acute encephalopathy in Japanese children in 1994-2002. *Virus Res* 103: 75-78.
23. Centers for Disease Control and Prevention (CDC) (2009) Neurologic complications associated with novel influenza A (H1N1) virus infection in children - Dallas, Texas, May 2009. *Morb Mortal Wkly Rep* 24: 773-778.
24. Morishima T, Togashi T, Yokota S, Okuno Y, Miyazaki C, Tashiro M, Okabe N (2002) Encephalitis and encephalopathy associated with an influenza epidemic in Japan. *Clin Infect Dis* 35: 512-517.
25. Ito Y, Ichiyama T, Kimura H, Shibata M, Ishiwada N, Kuroki H, Furukawa S, Morishima T (1999) Detection of influenza virus RNA by reverse transcription-PCR and proinflammatory cytokines in influenza-virus-associated encephalopathy. *J Med Virol* 58 :420-425.
26. Goenka A, Lilleker J, Michael BD, Ledger E, Hart IJ, Absoud M, Chow G, Lunn M, McKee D, Peake D, Pysden K, Roberts M, Carrol ED, Lim M, Avula S, Solomon T, Kneen R (2014) Neurological manifestations of influenza infection in children and adults: Results of a national British surveillance study. *Clin Infect Dis* 58 :775-778.
27. Newland JG, Laurich VM, Rosenquist AW, Heydon K, Licht DJ, Keren R, Zaoutis TE, Watson B, Hodinka RL, Coffin SE (2007) Neurologic complications in children hospitalized with influenza: characteristics, incidence, and risk factors. *J Pediatr* 150: 306-310.

Corresponding author

Sevliya Öcal Demir, MD
 Diyarbakır Children Hospital
 Pediatric Infectious Diseases
 Yenişehir Mah. Mimar Sinan Cad. no:15, 21090
 Bağlar/ Diyarbakır, Turkey
 Mobile: +905063814056
 Fax: +90 412 229 01 47
 E-mail: sevliyademir@gmail.com

Conflict of interests: No conflict of interests is declared.