J Forensic Sci, January 2008, Vol. 53, No. 1
doi: 10.1111/j.1556-4029.2007.00604.x
Available online at: www.blackwell-synergy.com

CASE REPORT

Kristen K. Landi,[1] *M.D. and Andrea T. Coleman,*[1] *M.D.*

Sudden Death in Toddlers Caused By Influenza B Infection: A Report of Two Cases and a Review of the Literature*

ABSTRACT: Sudden fatal cases of influenza B infection in a 4-year-old girl and a 2-year-old boy are presented. Both children complained of abdominal pain without respiratory, neurologic or cardiac symptoms; additionally the girl had vomiting within 2 days of death. Autopsy revealed histological changes in the respiratory system consistent with a viral infection. Influenza B infection was identified by immunohistochemistry in the girl and real-time polymerase chain reaction in the boy. Additional testing including cultures, toxicology, and screening for metabolic disorders were negative. These cases illustrate the usefulness of viral testing, especially for influenza, in the medical legal autopsy of children even when the classic respiratory symptoms of flu are lacking.

KEYWORDS: forensic science, forensic pathology, sudden death, viral infection, influenza, child, toddler

Influenza has historically been a cause of considerable mortality world wide, both during pandemics as well as during small outbreaks. It continues to be a significant cause of death today, especially among the very young, the very old and the immunocompromised (1–3). Influenza typically appears during the winter months. Classic symptoms include fever, sore throat, sweating, nasal obstruction, cough and myalgias (3). In severe cases bronchiolitis and pneumonia may be caused directly by the virus or may result from secondary bacterial invasion of the lungs. Influenza is caused by myxovirus influenzae, a single-stranded RNA virus, and there are three distinct serotypes (A, B and C), each containing antigenic strains (4). Virus A causes both pandemics as well as local outbreaks. It affects all age groups, and is associated with a high mortality in the elderly, the very young, and those with pre-existing cardiac and pulmonary disease (4). Virus B causes sporadic cases and limited epidemics, especially among institutionalized young people. It tends to cause a milder disease with a lower mortality rate (4). Virus C is occasionally detected in local outbreaks (4). There are few reported cases of influenza causing sudden death in children and almost all of these cases have been due to Influenza A. Here we present two cases of sudden death in toddlers due to Influenza B.

Case 1

A 4-year-old white girl with normal birth history and development, a past medical history of facial swelling after her MMR vaccination one and a half years prior to her death, and was currently undergoing testing for seasonal allergies. She lived with her parents and a younger brother. Her mother had a cough and cold type symptoms over the last week. She attended school regularly where the last reported infectious outbreak was a respiratory illness 3 months prior. She was in good health until 2 days before her death, when she developed abdominal pain and intermittent vomiting. Her vomitus was described by her mother as mucus and non-bloody. She refused to eat but did drink liquids. She was last seen alive by her parents at 3:30 AM when she complained of abdominal pain; she then vomited, urinated, and was placed back in bed. She was found dead in her bed at 7:30 AM by her father.

The autopsy yielded no significant gross findings, was negative for trauma, and showed normal development with all measurements and weights consistent with age. Neuropathological examination of the brain showed slight swelling and vascular congestion without gross or histological evidence of infection. Cultures of the blood and cerebrospinal fluid and swabs of the brain and middle ears were noncontributory. Toxicology was negative and vitreous humor chemistry did not show a dehydration pattern. Microscopic examination of the lungs revealed a chronic mixed inflammatory infiltrate involving the bronchioles, bronchi, and trachea consistent with a viral infection as well as multiple foci of mixed inflammation, including neutrophils and macrophages consistent with bronchopneumonia. Immunohistochemical testing using immunoalkaline phosphatase technique was performed using mouse monoclonal anti-influenza A virus and anti-influenza B virus antibody. Mouse monoclonal anti-influenza B virus antibody was strongly positive in the nuclei and cytoplasm of respiratory epithelial cells lining the trachea, bronchi, bronchioles, and in the detached necrotic debris within the lumens of the airways (Fig. 1). Mouse monoclonal anti-influenza A virus antibody was negative. Appropriate positive and negative controls were run in parallel. Gram and Steiner's stains showed abundant extracellular mixed bacterial flora consistent with postmortem overgrowth. Histology of the remaining organs including the heart was unremarkable. Immunohistochemical testing of the heart for influenza A and B was negative.

Case 2

A healthy 2-year-old boy with a normal birth history and development spent an uneventful day with his family visiting a museum in New York City. That evening he woke from a nap and declined

[1]Office of the Chief Medical Examiner, 520 First Ave, New York, NY 10016.

*Presented as a poster at the American Academy of Forensic Science Meeting, Seattle, WA, February 2006

Received 17 Feb. 2007; and in revised form 1 June 2007; accepted 3 June 2007.

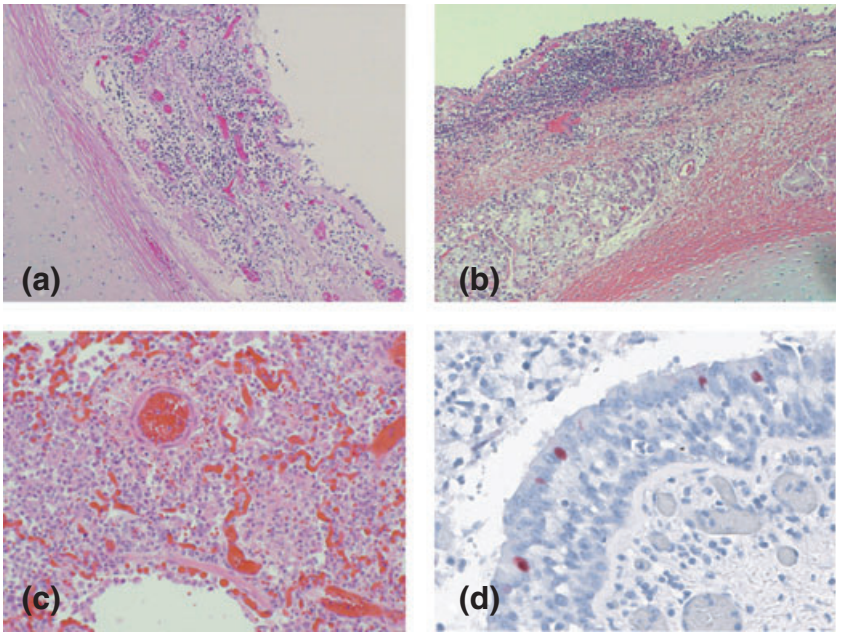

FIG. 1—*(a)Chronic inflammation in the tracheal mucosa of the boy. (b) Chronic inflammation in the bronchial mucosa of the girl. (c) Focal bronchopneumonia in the lungs of the girl. (d) Mouse monoclonal anti-influenza B virus antibody strongly positive in the nuclei of respiratory epithelial cells of the girl. [Hematoxylin and eosin stain, original magnification ×100 (a, b and c), ×400 (d).]*

dinner complaining of a stomach ache. His father noted that his abdomen was "bloated," but there was no attendant vomiting or diarrhea. Two hours later, he was bathed, nursed and placed supine in his parents' bed. Two and a half hours later, his father went to transfer him to his crib for the night where he found him prone; when he picked him up he was unresponsive and apneic. CPR was initiated and EMS was called. He had experienced slight "flu-like symptoms" over the past month for which he received Children's Tylenol® (McNeil Consumer and Speciality Pharmaceuticals, Forte Washington, PA) and Benadryl® (Pfizer, New York, NY).

The autopsy revealed good nourishment and hydration, normal development with measurements and weights consistent with the given age and minor resolving trauma indicative of an active toddler. Internal examination revealed moderate mesenteric and hilar lymphadenopathy, prominent white pulp of the spleen, and mucosal granularity of the terminal ileum that histologically represented follicular hyperplasia. The serosal surface of the bowel was pink and glistening. Neuropathologic examination showed slight cerebral edema. Cultures of cerebrospinal fluid, blood, and middle ear swabs were negative and noncontributory. Toxicology showed trace amounts of acetaminophen. Microscopic examination of the trachea and lungs showed a chronic inflammatory infiltrate of the bronchial and tracheal mucosa (Fig. 1). Microscopic examination of the heart, including the conduction system was unremarkable. RT-PCR for influenza A and influenza B viruses from the tracheal swabs were run with detection of influenza B virus RNA.

Discussion

Most of the rapid cases of influenza infection in children and adults associated with a rapid clinical course are caused by influenza A (5–7). The majority of the influenza associated deaths are among the elderly with 90% occurring among persons aged 65 years or older (1). During the 1990s, influenza was associated with 66 respiratory and circulatory deaths annually in the United States among children aged 1–4 years. Of these cases 17 were because of Influenza B infection. During this same time period over 32 000 deaths were caused by influenza among persons aged 65 years or older with over 4700 because of influenza B infection (1).

The largest case series of fatal influenza among children was presented by the Influenza Special Investigations Team at the Center for Disease Control in the New England Journal of Medicine (2). During the 2003–2004 influenza season, there were 153 reported cases of children dying from influenza in the United States. Of these 153 cases, 66 (43%) of them were in children ages 1–4 years of age. In all, 70 (47%) had been previously healthy without any high-risk medical condition such as asthma, or chronic illnesses. In all, 45 (29%) children died within 3 days after onset of illness and 8 (5%) died within 1 day. The most common clinical feature was fever, followed by respiratory symptoms; while 39% of children reported vomiting and only 6% had vomiting without respiratory symptoms. Of the 153 children 126 had influenza virus type determination with 123 (98%) being due to influenza A and 3 (2%) due to influenza B.

Children with influenza B infection may be the most likely group to have an atypical presentation. Extrapulmonary symptoms are more common among patients with infections caused by influenza B than among those with infections caused by influenza A virus (8). Gastrointestinal symptoms, including vomiting, abdominal pain, and diarrhea, are more common in children with influenza than in adults (9).

There are two main histological patterns in the lungs with viral infection. First is an acute bronchitis with predominantly lymphocytic inflammation as well as epithelial necrosis with plugging of the bronchiolar lumen (10). The second pattern is an interstitial pneumonia with expansion of the interstitial septae by chronic inflammation (10). Florid cases may also have widespread inflammation and necrosis of lung parenchyma. With a secondary bacterial infection a superimposed bronchopneumonia with acute inflammatory cells may also be present (10).

While the mechanism of death in rapidly fatal influenza infections is still unknown, there is ongoing research into the possible

role of an over-responsive immune system. The generated immunological response is believed to cause additional injury in a number of infections including influenza associated encephalopathy, streptococcal toxic shock syndrome and RSV respiratory infections (3,11). Immune mediated injury may also result from the cytokine storm triggered by the initial infection which then spills over into the systemic circulation to cause devastating consequences in a relatively short period of time. It has been suggested that RNA viruses like influenza may be more likely to result in an inappropriate or overzealous host response (12) including cytokine and chemokine upregulation involving numerous interleukins (including IL-1, IL-6, IL-8), tumor necrosis factor and chemokine MIP-1 (3,11,13,14). Atopic individuals appear to be over-responders to infections and are more likely to release proinflammatory mediators (11,13). While immune-mediated injury caused by an otherwise mild infection from a histological standpoint may explain the sudden deaths in these two cases with few findings at autopsy, continued research is needed to elucidate these pathways. There is also no easy way to test for cytokine storm at postmortem.

The current primary defense against influenza is largely preventative through vaccination. The vaccine is only *c.* 68% effective in preventing deaths from complications of influenza infection and there have been reported deaths in children who have been vaccinated (2,11). The CDC influenza special investigation team found influenza fatalities still occurred despite the fact that 26% of high-risk children and 19% of healthy children had received at least one dose during the 2003–2004 seasons (2). While the use of antiviral medication in the fatal influenza cases has not been specifically reported, the CDC did find that 90 children (59%), including 85 who had been admitted to an intensive care unit, died after hospital admission, despite all therapy (2). There is ongoing research looking into the possible role of using immunomodulators as part of the medical treatment of influenza to help prevent cytokine storm and its possible sequelae.

These cases highlight the need for specialized testing in pediatric autopsy cases, more specifically the need for viral testing, especially for influenza. These cases illustrate two atypical cases of influenza B infection with rapidly fatal outcomes, which would not have been suspected based on the presenting symptoms. Similar cases may be detected if viral cultures are performed in similar types of cases. Cases of sudden death among children, especially with atypical symptoms for influenza, usually do not get viral studies collected at the time of autopsy and if viral infections are not considered the cause of death may remain elusive. We recommend screening cases of sudden death among infants and children for viruses in addition to the more standard specialized testing such as bacterial cultures.

Acknowledgments

We thank Dr. Christopher Paddock and the Center for Disease Control for performance of immunohistochemical assays and for providing pictures and Dr. Iqbal Poshni at the New York City Department of Health and Mental Hygiene Public Health Labs for performance of the real-time polymerase chain reaction. We would also like to thank Howard Mittelmark for his help with copyediting.

References

1. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003;289(2):179–85.
2. Bhat N, Wright JG, Broder KR, Murray EL, Greenberg ME, Glover MJ, et al. Influenza-associated deaths among children in the United States, 2003–2004. N Engl J Med 2005;353(24):2559–67.
3. Snelgrove R, Williams A, Thrope C, Hussell T. Manipulation of immunity to and pathology of respiratory infections. Expert Rev Anti-infect Ther 2004;2(3):413–26.
4. Emond RTD, Welsby PD, Rowland HAK. Color atlas of infectious diseases, 4th edn. New York: Mosby, 2003.
5. Ishigami A, Kubo S, Ikematsu K, Kitamura O, Tokunaga I, Gotohda T, et al. An adult autopsy case of acute encephalopathy associated with influenza A virus. Legal Med 2004;6:252–5.
6. Tsokos M, Zollner B, Feucht HH. Fatal influenza A infection with Staphylococcus aureus superinfection in a 49-year-old woman presenting as sudden death. Int J Legal Med 2005;119:40–3.
7. Thomas P, Riffelmann M, Schweiger B, Dominik S, Wirsing von Konig CH. Fatal influenza A virus infection in a child vaccinated against influenza. Pediatr Infect Dis J 2003;22(2):201–2.
8. Xu H, Yasui O, Tsuruoka H, Kuroda K, Hayashi K, Yamada A, et al. Isolation of type B influenza from the blood of children. Clin Infect Dis 1998;27:654–5.
9. Wright PF, Bryant JD, Karzon DT. Comparison of influenza B/Hong Kong virus infections among infants, children, and young adults. J Infect Dis 1980;141:430–5.
10. Aherne W, Bird T, Court SD, Gardner PS, McQuillin J. Pathological changes in viral infections of the lower respiratory tract in children. J Clin Pathol 1970;23(1):7–18.
11. Welliver RC. Respiratory syncytial virus and other respiratory viruses. Pediatr Infect Dis J 2003;22:S6–12.
12. Mahalingam S, Meanger J, Foster PS, Lidbury BA. The viral manipulation of the host cellular and immune environments to enhance propagation and survival: a focus on RNA viruses. J Leukoc Biol 2002; 72:429–39.
13. Message SD, Johnson SL. Host defense function of the airway epithelium in health and disease: clinical background. J Leukoc Biol 2004;75:5–17.
14. Kaiser L, Fritz RS, Straus SE, Gubareva L, Hayden FG. Symptom pathogenesis during acute influenza: interleukin-6 and othe cytokine responses. J Med Virol 2001;64:262–8.

Additional information and reprint requests:
Kristen Landi, M.D.
Office of the Chief Medical Examiner
520 First Avenue
New York, NY 10016
E-mail: klandi@ocme.nyc.gov