

copy and nasal wash specimens from patient 4 also were negative for such antigens on laboratory testing. This underscores the limitations of current testing and that the sensitivity of pandemic (H1N1) 2009 diagnostic testing remains poor and needs further improvement. Thus, in patients suspected of having pandemic (H1N1) 2009 or in those who are critically ill, lower tract respiratory specimens should be tested to improve diagnostic sensitivity, and clinicians should consider using immunoassay and culture methods.

All 4 patients described in this case series had viral isolates containing H275Y mutation in the neuraminidase gene of pandemic (H1N1) 2009 virus, which is specifically associated with high-level resistance to oseltamivir. Increasing data show that immunocompromised patients are at increased risk for development of drug-resistant influenza infections after oseltamivir prophylaxis or while receiving oseltamivir treatment (6). Fortunately, this resistance trait remains rare.

Existing evidence suggests oseltamivir-resistant pandemic (H1N1) 2009 virus is stable and retains similar transmissibility and virulence as the wild-type virus (7). Therefore, in immunosuppressed patients, in which the influenza mortality rate is high, clinicians should also suspect drug-resistant influenza infection if the patient does not improve. Before she died of underlying hematologic illness, patient 2 clinically improved after treatment with intravenous zanamivir (obtained through an emergency application for an investigational–new drug). As reported in other studies, pandemic (H1N1) 2009 virus was found in her nasal washes, 1 week after she received zanamivir for 10 days (8).

Some data suggest that pandemic (H1N1) 2009 virus has a predilection to affect the lower respiratory tract and is associated with more illness and death than is seasonal influenza

(9). All 4 case-patients in this series developed dyspnea, and 3 of the 4 ultimately died of refractory respiratory failure. Our observations suggest that oseltamivir-resistant pandemic (H1N1) 2009 virus is also associated with poor prognosis and may retain the same tropism for lower respiratory tract involvement as wild type.

These case-patients illustrated the complexity of the diagnosis and management of such infections in hospitalized immunocompromised patients. Vigilance and heightened clinical suspicion are needed to facilitate early diagnosis, treatment and prevention measures to limit transmission of pandemic (H1N1) 2009 virus or similar viral pathogens.

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DOI: 10.3201/eid1611.101053

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Acute Encephalopathy and Pandemic (H1N1) 2009

To the Editor: Since the World Health Organization declared a global pandemic of influenza A pandemic (H1N1) 2009 in June 2009, the number of cases of this strain of influenza has steadily risen. Although most cases have been mild, with complete and uneventful recovery, multiple cases of severe infection with complications, including death, have been reported. Yet the neurologic complications of this virus have been rarely described. We read with interest the article by Kitcharoen et al. (1) concerning a patient with encephalopathy associated with pandemic (H1N1) 2009, which

progressed to produce quadriplegia with diffuse sensory loss. In that study, however, pandemic (H1N1) 2009 virus was not isolated from the patient's cerebrospinal fluid (CSF) or brain tissue or detected by reverse transcription–PCR (RT-PCR). We report a case in an adolescent patient with encephalopathy-associated pandemic (H1N1) 2009 that was confirmed by real-time RT-PCR of CSF.

On November 2, 2009, a previously healthy 16-year-old girl was admitted to Asan Medical Center, Seoul, South Korea. Five days earlier, she had sought care for cough, fever (maximum 38.5°C), and mild headache. Enzyme immunoassay (SD Bioline rapid influenza test; Standard Diagnostics Inc., Yongin, South Korea) of a nasopharyngeal swab was positive for influenza virus. Because a large outbreak of pandemic (H1N1) 2009 was concurrent, she was given a presumptive diagnosis and treated with oseltamivir, 75 mg 2×/d, for 5 days. However, her headache worsened, and she was referred to the hospital.

At admission, her temperature was 36.8°C. Examination showed no disturbance of consciousness or focal neurologic deficits except for a severe headache. Results of routine laboratory tests, including serologic tests for HIV, were negative. Real-time

RT-PCR of a nasopharyngeal swab at admission was negative for pandemic (H1N1) 2009 virus; a serologic test for this virus was not performed. A magnetic resonance imaging (MRI) scan of the patient's brain at admission is shown in the Figure, panel A. Examination of CSF showed 0 cells/mm³, protein 35.4 mg/dL, glucose 48 mg/dL; blood glucose level was 49%. No bacteria or fungi were isolated from CSF, but pandemic (H1N1) 2009 virus was detected by real-time RT-PCR (Roche Diagnostics, Mannheim, Germany). On the basis of the MRI and RT-PCR results, we diagnosed encephalopathy-associated pandemic (H1N1) 2009 infection. By hospital day 3, her headache and respiratory symptoms had improved, and she was discharged on day 10 without headache or other neurologic signs. A follow-up brain MRI, obtained 1 month later, is shown in the Figure, panel B.

Several hypotheses have been proposed regarding the pathogenesis of influenza-associated acute encephalopathy (IAAE) (2): the most straightforward is that it is caused by viral infection of the central nervous system. The isolation of influenza virus from the CSF of living patients (3) (or its detection by RT-PCR) and from brain tissue of patients who have died (4) supports this hypothesis. More fre-

quently, however, influenza virus has not been detected in the CSF or brains of affected patients despite thorough attempts. Thus, other possible methods for the assessing the pathogenesis of IAAE have been proposed: elevated concentrations of several cytokines such as interleukin (IL)–6, tumor necrosis factor (TNF)– α , and soluble TNF receptor-1; or determination of renal and hepatic dysfunction (2). Although IAAE in adults and children was reported during the pandemic (H1N1) 2009 pandemic (1,5–8), this virus was not detected by virus isolation or RT-PCR in CSF and brain tissue of these patients. The virus was detected in CSF of an infant 3 months of age with IAAE (8); however, the virus may have been found in CSF because of the presence of blood from a traumatic lumbar puncture.

The absence of pleocytosis and the normal protein and glucose levels in CSF from the patient described here were noteworthy. Previous reports showed that leukocyte counts within normal limits (70%–90%) were found in CSF of patients with IAAE and seasonal influenza infection (9,10). Recent publications on IAAE and concurrent pandemic (H1N1) 2009 virus infection also reported no increase in CSF leukocyte count and protein level (1,5,7). Therefore, absence of CSF pleocytosis and protein levels within normal limits are common with IAAE.

The diagnosis of IAAE in the patient reported here is probable, based on positive real-time RT-PCR results from CSF examination and brain MRI findings. However, some limitations should be mentioned. First, a positive RT-PCR result could have resulted from contamination associated with clinical procedures and laboratory assays. Nonetheless, we believe that the lumbar puncture was done aseptically and that the real-time RT-PCR performed in the hospital's clinical microbiologic laboratory was reliable. Second, the brain MRI findings were also nonspecific and could be associ-

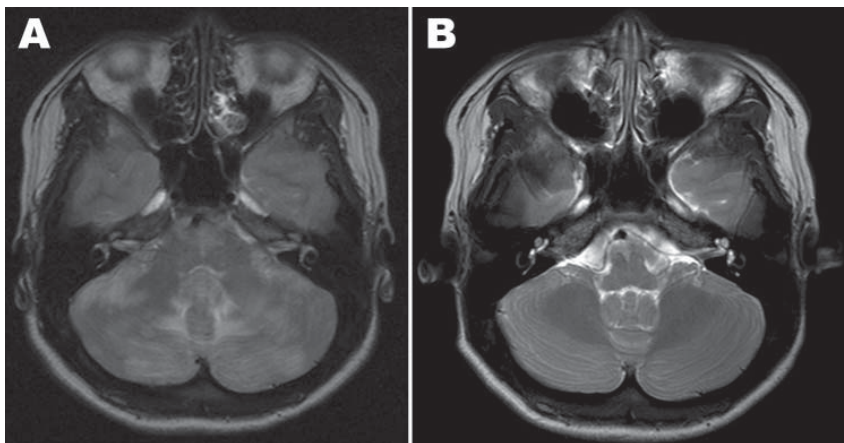


Figure. Magnetic resonance imaging (MRI) scans of case-patient's brain. A) MRI at hospital admission shows ill-defined T2 changes in both cerebellar hemispheres, periventricular white matter, and the pons. B) MRI of the brain 1 month later, showing nearly complete disappearance of the changes observed at admission.

ated with hypoxia, edema, or other unknown processes. However, the patient had no history of hypotensive episodes, hypoxemia, abnormal metabolic and toxic processes, and other infectious disease. In conclusion, IAAE with pandemic (H1N1) 2009 may be caused by direct viral infection of the CNS and, although its pathogenesis is not clear, physicians should remain alert to this possibility.

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DOI: 10.3201/eid1611.100682

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Oseltamivir-Resistant Pandemic (H1N1) 2009 Treated with Nebulized Zanamivir

To the Editor: In late November 2009, a 3-year-old immunocompromised boy experienced an upper respiratory tract infection caused by influenza A pandemic (H1N1) 2009 virus, as demonstrated by a positive result for real-time PCR on a nasal swab specimen. His medical history was notable for a congenital intracardiac tumor; an ABO-incompatible heart transplant at 2 months of age; and an Epstein-Barr virus-related humoral rejection 20 months later that was treated with anti-CD20 and plasmapheresis and continuous immunosuppressive ther-

apy with tacrolimus and everolimus. Thus, a 5-day regimen of oseltamivir treatment was undertaken, and the patient's clinical signs improved.

However, 3 days after drug treatment was suspended, the child had a relapse and exhibited fever, cough, and mild respiratory distress. The patient had fine crackles in the left posterior basal lung, normal oxygen saturation, and an infiltrate in the left basal lung, observed on chest radiograph. Infection with pandemic (H1N1) 2009 virus was confirmed. He was then transferred to an isolated ward of the pediatric department, and oseltamivir treatment was again initiated and dosages of immunosuppressive drugs were reduced. However, no clinical or virologic responses were observed during the 3 weeks of drug administration.

Over the next month, the oral dosage of oseltamivir was increased twice, without substantial effects on clinical course and viral clearance of the infection (Figure). Because of persistence of infection, the viral neuraminidase gene was sequenced, which showed the H275Y mutation (1). We immediately requested zanamivir aqueous solution from GlaxoSmithKline (Brentford, UK), and, after the approval of the hospital's ethics committee and parents' consent were obtained, nebulized treatment was carried out for 10 days. Fever and respiratory symptoms and signs resolved after 6 days of treatment and progressive real-time PCR gave negative results. Moreover, at the end of the treatment period, chest radiograph did not show abnormal findings, and results of a hemagglutination-inhibition assay were positive for influenza. No zanamivir-related adverse events were observed, except for a mild bronchospasm that responded to albuterol.

Another notable point is that the clinical course of the disease was not severe, although the child was immunocompromised and the infection persisted for almost 2 months. However,