Successful Treatment of Influenza-Associated Acute Necrotizing Encephalitis in an Adult Using High-Dose Oseltamivir and Methylprednisolone: Case Report and Literature Review

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A case of influenza-associated acute necrotizing encephalitis (ANE) is described in an otherwise healthy adult. The patient was treated successfully with a combination of high-dose methylprednisolone and high-dose oseltamivir. The patient relapsed after discontinuing 150 mg twice daily oseltamivir but quickly improved and eventually recovered after reinitiation of high-dose oseltamivir for an additional 2 weeks. The clinical presentation, pathogenesis, and treatment of influenza-associated ANE is reviewed. The use of high-dose oseltamivir in combination with methylprednisolone may offer additional therapeutic benefit for this rare and poorly understood complication of influenza infection.

Keywords: acute necrotizing encephalitis; encephalitis; encephalopathy; influenza; oseltamivir.

Acute necrotizing encephalitis (ANE) was first described in 1995 by Mizuguchi et al [1] after examining the records of Japanese children diagnosed with encephalitis associated with influenza infection in East Asia. During subsequent influenza outbreaks and pandemics, ANE was noted repeatedly in the pediatric populations, with a striking predominance among Japanese children [2, 3]. In contrast, there are only 4 published cases of influenza-associated ANE occurring in the adult population [4–7]. In this study, we report a successfully treated case of severe influenza-associated ANE in a previously healthy 46-year-old man.

METHODS

We describe the presentation, diagnosis, and treatment of an adult male with influenza-associated ANE. In addition, a narrative literature review was conducted regarding the diagnosis, pathogenesis, and treatment of ANE. Search terms using a PubMed query for articles published between 1945 and 2016 included the following: influenza, encephalitis, encephalopathy, H1N1, acute necrotizing encephalitis, cytokines, oseltamivir, efficacy, influenza-associated encephalopathy. In addition, a manual search using references from identified articles was also reviewed for relevant publications. Selected articles were screened for inclusion based on relevance and rigor. The patient’s written consent was obtained for publication.

Case Report

A 46-year-old male patient with no prior medical history presented in March 2016 with acute onset dry cough, sore throat, myalgia, and fever that developed 48 hours before admission. Family members reported that he became drowsy during the first day of illness, then more confused and weak the day after. There was no witnessed seizure activity at home or en route to the facility.

The patient resided with his wife and 3 children in Buffalo, New York. All household members had an influenza-like illness during the week. The patient worked in an office setting. He had no recent travel, contact with travelers, or animal exposures. He took no medications except acetaminophen for fevers. He was never vaccinated against influenza.

Upon presentation, all vital signs were within normal limits except for an oral temperature of 101°F. His neurological examination revealed generalized weakness and extreme drowsiness with moderate confusion. He demonstrated normal deep tendon reflexes and normal Babinski response bilaterally. There was no nuchal rigidity nor any other focal neurological deficits. The remainder of the physical examination was unremarkable.

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positive for influenza A (BinaxNOW; Alere Inc.). Lumbar puncture revealed an opening pressure of 12 cmH2O with clear, colorless cerebrospinal fluid (CSF). Analysis of CSF revealed an elevated protein at 78 mg/dL, 0 white cells, 0 red blood cells, and a glucose of 67 mg/dL.

A chest x-ray and noncontrast computed tomography (CT) of the head obtained on admission were both normal. On hospital day 1, a noncontrast magnetic resonance image (MRI) of the brain showed bilateral symmetrical areas of hemorrhagic infarctions within thalami and heads of caudate nuclei, with associated edema (Figure 1). Brain magnetic resonance angiography and magnetic resonance venography showed normal vasculature without thrombosis.

Later on, and within 24 hours of admission, the patient became completely unresponsive, requiring endotracheal intubation for airway protection. Chest imaging taken shortly after intubation revealed a new right lower lobe infiltrate, and treatment with levofloxacin and piperacillin-tazobactam was initiated for possible secondary bacterial versus aspiration pneumonia. There were no clinical or radiological signs of acute respiratory distress syndrome (ARDS) throughout the admission. Cerebrospinal fluid (CSF) and endotracheal aspirate fluid were submitted to the New York State Department of Health Laboratory (Wadsworth, NY) for multiple viral tests utilizing polymerase chain reaction (PCR). The CSF PCR panel was negative for herpes simplex virus (HSV1, HSV2, varicella-zoster virus, cytomegalovirus, human herpesvirus 6 (HHV-6), adenovirus, Epstein-Barr virus, West Nile virus, and enteroviruses. His CSF was also negative for immunoglobulin (Ig)G and IgM for West Nile virus, cryptococcal antigen, and venereal disease research laboratory. Serum samples were also negative for human immunodeficiency virus, syphilis, antinuclear antibody, and antineutrophil cytoplasmic antibody. Cultures from CSF, blood, and respiratory secretions were all negative. Hypercoagulability screening was negative too. Serum thiamine and folate levels were normal.

Nasopharyngeal and endotracheal aspirate specimens were positive for pandemic 2009 H1N1 influenza by PCR. However, the CSF sample for influenza PCR was negative. Continuous electroencephalogram showed diffuse slowing but no seizure activity. There was no evidence of vasculitis on cerebral angiogram.

Based on the characteristic MRI findings, clinical presentation, and lack of other clear etiology, a diagnosis of influenza A-associated ANE was made, and treatment with oseltamivir 75 mg twice daily was initiated. Two days later, the patient was also started on methylprednisolone pulse therapy (1 gram intravenous daily for 3 days), which was followed by a tapering dose of prednisone. However, the patient remained unresponsive during the first 5 hospital days with ongoing fevers up to 102°F. Repeat blood and respiratory cultures remained negative. On day 5, he developed decerebrate posturing with brisk patellar and bicep reflexes and abnormal Babinski response. No nuchal rigidity was noted. Due to the severity of his condition and failure to improve with initial management, the dose of oseltamivir was increased to 150 mg twice daily on hospital day 5.

Within 24 hours his mentation improved and decerebrate posturing ceased. His alertness increased gradually over the next several days with improved mentation. By hospital day 10 he was following commands and was extubated. After extubation, he was noted to have dysarthria and a restricted affect with slow reaction times and generalized weakness. High-dose oseltamivir was discontinued after 5 days due to his improved status, but prednisone was continued for 2 more days.

However, his symptoms of lethargy recurred over the following 3 days. Brain MRI was repeated at this point and showed the same lesions identified on the previously MRI but were more defined. High-dose oseltamivir treatment (150 mg twice daily) was restarted without reintroduction of steroids, and his alertness improved again within 24 hours.

Thus, high-dose oseltamivir was continued for a total of 15 additional days. On the 19th hospital day, he was awake, responsive, and following all commands. He was functionally back to his baseline with some residual short-term memory loss and mild ataxia by the end of an acute physical rehabilitation.
stay, 49 days after his initial presentation. One year later, the
patient had full recovery of his motor and over all functionality,
except for infrequent episodes of difficulty finding words and
decreased motivation.

DISCUSSION

Influenza virus infection is associated with a wide range of neu-
rological complications including Reye syndrome, generalized
encephalopathy, seizure, asctic meningitis, and postinfectious
acute disseminated encephalomyelitis [8, 9]. Acute necrotizing
encephalitis is another distinct neurological complication of
influenza infection with reported mortality rates of 30%–40%
[1, 2, 10], second only to historical descriptions of encephalitis
lethargica (60%) among neurologic complications of influenza
[10].

Clinical Presentation, Diagnosis, and Outcome

Acute necrotizing encephalitis is almost exclusively reported
in pediatric populations, beginning with Mizuguchi’s [1, 2]
description of Japanese children in 1995 [3]. Reports of ANE
seem to have 2 distinct patterns. In the first scenario, patients
suddenly develop deterioration in mentation after presenting
with severe influenza infection complicated by other organ dys-
function such as acute lung injury, disseminated intravascular
cogulation (DIC), or shock [7]. In the second scenario, exem-
plified in this case report, systemic illness is less pronounced,
and altered sensorium is often the initial manifestation leading
to medical evaluation [11].

In many cases, the distinctive rapid onset of lethargy associated
with ANE often appears within 2 days of influenza-like illness
symptoms [3, 12, 13]. The clinical course is characterized by a
rapidly progressive encephalopathy, with associated vomiting
and lethargy. Seizures often develop early in the most affected patients
[14]. Deep coma requiring mechanical ventilation usually ensues
several hours to 1 day from start of neurological symptoms. In
severe cases, widespread brain edema can be life-threatening [3, 11, 13].
Elevated opening pressures may be seen on lumbar puncture,
but CSF analysis usually reveals normal cell counts and glu-
cose levels, occasionally with mild elevation of protein levels [15, 16].
It is notable that influenza virus was not isolated from CSF or
brain tissue in most reports [3, 4, 13].

Brain imaging demonstrates the hallmark findings of ANE. Ini-
itially, brain CT may show hypodense areas within thalamus
bilateral. Magnetic resonance imaging exam shows character-
istic symmetrical bilateral hyperintense signals at both thalami,
only most apparent within the caudate heads, and putamen
with features of necrosis as time progresses. Involvement of
other brain regions is less commonly reported, although cere-
bellar and brainstem lesions have been described [17].

The mortality of influenza-associated ANE is commonly
reported to be approximately 30%–40% throughout litera-
ture [1, 2, 10]. Survivors are left with significant permanent
neurological sequelae in approximately 40% of cases, with the
residual neurologic deficits correlating with involved areas of
the brain [2].

Pathogenesis

Acute necrotizing encephalitis is linked to influenza virus infec-
tion in many cases. Yet, in several reports, there were no causa-
tive pathogens identified. In a few cases, ANE was thought to
have been caused by other pathogens such as HHV-6, measles,
and mycoplasma [2, 18, 19].

The pathogenesis of ANE is not fully understood. Autopsy
specimens show necrosis with petechial hemorrhages in the
thalamus and tegmentum of the pons, as well as myelin pallor
in the cerebral and cerebellar deep white matter [20]. Vascular
endothelial pathology and surrounding vasogenic edema with-
out visible vascular occlusion have also been reported [15].
The absence of influenza virus in central nervous system (CNS)
specimens has led to the speculation that the triggering inflam-
atory insult originates outside the CNS. This was also sug-
gested in other studies, which reported serum cytokines levels
to be higher compared with levels measured within the CSF [21].

Some authors have hypothesized that disruption of the blood-
brain barrier in the settings of systemic cytokine storm may be
responsible for inducing the necrotic brain lesions observed in
ANE [22]. Accordingly, influenza virus does not directly invade
the CNS. Rather, significant inflammation elsewhere triggers
an abundant immune response culminating in the disruption of
the blood-brain barrier at localized areas, which eventually
leads to the characteristic brain lesions seen in ANE [23–25].
At their physiologic levels, cytokines, especially interleukin-6
and tumor necrosis factor-α, exert a protective effect against
invading pathogens. However, abnormally high cytokines levels
(ie, cytokine storm) could have a paradoxical neurotoxic effect
leading to disruption of the blood-brain barrier and subsequent
injury [26]. Such levels have been reported in cases with influ-
enza-associated encephalitis [4, 26, 27].

In contrast, conflicting observations from our case and from
earlier literature may suggest a primary insult within the CNS in
a subgroup of patients leading to the characteristic focal brain
tissue by culture or PCR in some patients [10, 29–32].

In our case, several observations raise the possibility of a pri-
mary neurological insult from influenza infection. First, neu-
rologic dysfunction ensued in the absence of other widespread
organ dysfunction such as shock, multiple organ failure, DIC, or
ARDS—making an overwhelming systemic insult an unlikely trig-
grer for the rapid onset focal brain necrosis observed. Second, our
patient failed to show improvement on standard doses of oseltam-
ivir, but he improved shortly after using high-dose oseltamivir.

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Furthermore, symptoms recurred within 72 hours of discontinuation of high-dose oseltamivir, but they quickly resolved after restarting high-dose oseltamivir, which can indicate an ongoing viral brain insult. It is notable that the patient was still receiving steroids when the high-dose oseltamivir treatment was interrupted, but his second improvement phase occurred after restarting high-dose oseltamivir without reintroduction of steroids.

**Management**

At this time, there is no definitive treatment for ANE. Management relies largely on supportive care, including treatment of seizures, and increased intracranial pressure, if present. Intravenous corticosteroids, antivirals (eg, oseltamivir), and gammaglobulins are the most commonly reported therapies used [11, 18, 33]. The Research Organization for Influenza Encephalopathy Researchers in Japan described the benefits of methylprednisolone pulse therapy in patients with influenza-associated encephalitis. Although there was no significant difference in efficacy noted between methylprednisolone pulse therapy and intravenous dexamethasone, a clear correlation was established between better outcomes and the early administration (within 24 hours) of intravenous steroid therapy [34].

Several studies support the use of oseltamivir in complicated influenza infection, including those with neurological manifestations [35–37]. Oseltamivir’s ability to cross blood-brain barrier was found to be low in healthy volunteers [38]. The penetration of oseltamivir, particularly at higher doses, within inflamed and injured brain tissue is not described. Despite this, higher doses of oseltamivir have been used with benefit when treating influenza infections in animals [39]. One report noted favorable outcomes using prolonged high-dose oseltamivir treatment along with the use of intravenous steroid therapy and gammaglobulins in a case of influenza encephalitis [11].

Gammaglobulin and plasma exchange have been used to treat selected ANE cases with variable degrees of improvement [11, 34]. The use of other immunosuppressive medications are under study [11, 34]. The Research Organization for Influenza Encephalopathy Researchers in Japan described the benefits of methylprednisolone pulse therapy in patients with influenza-associated encephalitis. Although there was no significant difference in efficacy noted between methylprednisolone pulse therapy and intravenous dexamethasone, a clear correlation was established between better outcomes and the early administration (within 24 hours) of intravenous steroid therapy [34].

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**CONCLUSIONS**

Acute necrotizing encephalitis is a rare and serious neurologic complication of influenza infection characterized by rapid decline in mentation coupled with imaging findings of symmetrical necrotic injury within the thalamus and adjacent structures. Along with supportive care, early use of high-dose corticosteroids and high-dose oseltamivir may lead to lower mortality with fewer long-term sequelae of disease. To the best of our knowledge, our patient is the fifth adult with influenza-associated ANE described in the literature, and the first adult to survive ANE in the United States.

Further studies are needed to characterize the specific pathogenesis of ANE and to better inform optimal management. Our experience suggested that the use of high-dose oseltamivir correlated with improved mentation and resolution of symptoms. The discontinuation of high-dose oseltamivir was followed by recurrence of symptoms with a second resolution after reintroduction of high-dose therapy. Based on these findings, we propose the use of high-dose oseltamivir for at least 14 days in patients with influenza-associated ANE, in addition to early use of corticosteroids and supportive care. Although vaccination against influenza virus has been shown to limit its morbidity and mortality in general [40], it has not been shown to directly affect morbidity and mortality from ANE specifically.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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