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Case Report

Influenza-Associated Acute Necrotizing Encephalopathy: An Illustrative Case Amidst the Severe United States 2024-25 Influenza Season

Katherine Thomas [1] and Andrew Silverman [2,*]

[1] Pediatric Rehabilitation Medicine, Santa Clara Valley Medical Center, Santa Clara CA

[2] Pediatric Neurology, Stanford Children's Hospital, Palo Alto CA

* Correspondence: aesilver@stanford.edu

Abstract: Acute necrotizing encephalopathy (ANE) is a rare, fulminant encephalopathy associated with viral infections, such as influenza, characterized by multifocal symmetric brain lesions and cytokine-mediated neuroinflammation. A 6-year-old previously healthy female, fully vaccinated except for the seasonal influenza vaccine, presented with fever, sore throat, cough, and worsening altered mental status. Neurological examination revealed a Glasgow Coma Scale (GCS) of 6, abnormal brainstem reflexes, and subsequent seizure activity, ultimately necessitating intubation. Initial laboratory findings were notable for hyperglycemia, ketonuria, and elevated cerebrospinal fluid (CSF) protein, while brain magnetic resonance imaging (MRI) demonstrated characteristic bilateral thalamic, brainstem, and cerebellar lesions. Continuous electroencephalography (EEG) showed diffuse slowing without epileptiform discharges. Empirical treatment included broad-spectrum antibiotics, antiviral therapy (oseltamivir), high-dose corticosteroids, and intravenous immunoglobulin (IVIg). The patient required prolonged ventilatory support and experienced significant motor dysfunction, hypertonicity, and disorder of consciousness for approximately one month. A follow-up MRI showed evolving encephalomalacia and atrophy, particularly in the frontal lobes, hippocampi, and basal ganglia. After a subsequent month of inpatient rehabilitation, she demonstrated substantial functional improvement, regaining the ability to walk short distances with assistance, communicate verbally, and resume oral feeding. However, persistent deficits in cognitive processing speed, problem-solving, vision, and motor control remained. This case highlights the severity of influenza-associated ANE and its potential for lasting neurological impairment. Although no standardized treatment protocol exists, immunomodulatory therapies such as corticosteroids and IVIg are widely used based on the presumed role of cytokine dysregulation. Early recognition and aggressive supportive care are critical in ANE management. Intensive neurorehabilitation plays a key role in optimizing functional outcomes, though long-term deficits may persist. This case brings up key and timely questions about the importance of influenza vaccination in preventing severe neurological complications. Notably, anecdotal reports indicate increased cases of influenza-associated encephalopathy in recent flu seasons, emphasizing the need for heightened clinical awareness and further research into prognostic markers and treatment strategies.

Keywords: influenza; vaccination; neurology; infectious disease; encephalopathy; acute necrotizing encephalopathy

Case

A 6-year-old, previously healthy female, fully vaccinated apart from not having received the seasonal influenza vaccine, presented for medical evaluation after 5 days of fever, sore throat, cough, and approximately 12 hours of worsening altered mental status as well as generalized weakness. Her birth, developmental, medical, surgical, and family histories were unremarkable. She had not taken any medications or supplements recently and had no known allergies. There were toxic exposures.

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On initial arrival in the emergency department, she was tachycardic but other vitals were within normal limits. Initial neurologic examination reflected a GCS of 6 marked by lethargy and minimal responsiveness to sternal rub. Pupils were reactive and equal bilaterally. There were no spontaneous extraocular movements; oculocephalic reflex was absent. Plantar reflex showed up-going toes on the left and down-going toes on the right. Her course in the emergency department was additionally notable for two generalized tonic-clonic convulsions, which resolved after intravenous lorazepam and subsequent levetiracetam administration. This sequence of events, in combination with her poor neurologic exam, precipitated respiratory failure, necessitating intubation and mechanical ventilation. Continuous electroencephalography showed diffuse slowing consistent with ongoing encephalopathy, but no epileptiform discharges or seizures.

Initial laboratory evaluation was significant for elevated urine ketones to 40 mg/dL, urine protein elevated to 30 mg/dL, hyperglycemia to 142 mg/dL, and positive influenza A antigen testing. Serum lactate and liver function tests were within normal limits (AST 30, ALT 11 U/L). Platelets were normal as well (222 k/μL). CRP was <0.3 mg/dL. Initial chest x-ray showed perihilar and peri-bronchial thickening, consistent with bronchiolitis, but otherwise no focal consolidations. Cerebrospinal fluid (CSF) analysis revealed 18 white blood cells/uL, 418 red blood cells/uL, glucose 70 mg/dL, and elevated protein to 144 mg/dL. CSF bacterial cultures showed no microbial growth. Her serum interleukin-6 level was within normal limits.

Brain magnetic resonance imaging (MRI) with and without contrast was obtained on the first day of hospitalization, which showed multiple foci of restricted diffusion and increased T2 FLAIR signal seen most prominently in the bilateral insula, hippocampi, thalami, mamillary bodies, ventral pons, periaqueductal grey mater, medulla, and cerebellar vermis (Figure 1). Additional scattered, hyperintense lesions were noted throughout the cerebral cortex, although the occipital lobes were spared. As noted, electroencephalography (EEG) showed moderate diffuse slow background; sleep spindles were present. Overall, her clinical presentation, imaging, and laboratory results were felt to be most consistent with a viral encephalitis in the setting of her ongoing influenza A infection – namely, acute necrotizing encephalopathy (ANE). Genetic predisposition syndromes have been described, but genetic testing was not sent for this patient. The ANE severity score was 5 for brainstem lesions, age, and CSF protein count.

She was empirically treated with meningitis-dose ceftriaxone, acyclovir, vancomycin, and completed a 6-day course of oseltamivir. For ANE, she received a 4-day course of 30 mg/kg/day methylprednisolone, followed by a corticosteroid taper over the subsequent 4 weeks. She also received a 2-day course of intravenous immunoglobulin (IVIg 2 g/kg), and neurology consultation recommended continuing levetiracetam.

During her one-month acute hospitalization, she required intubation and ventilatory support for 7 days as well as nasogastric tube placement to facilitate enteral nutrition. She developed diffuse hyperreflexia and spasticity in all extremities. She was eventually transitioned out of the pediatric intensive care unit to the general pediatrics ward at hospital day 10, where she continued to have a critical disorder of consciousness for approximately one month. By the time of her acute hospital discharge at hospital day 30, she had improved to being minimally conscious. Upper extremity hypertonicity as well as hyperreflexia had improved. However, significant spasticity persisted at her bilateral plantarflexors. Her modified Rankin scale (mRS) at days 7, 30, and 90 were 5, 5, and 3, respectively.

A follow-up brain MRI with and without contrast was obtained 23 days after her initial brain MRI and showed improvement in the FLAIR hyperintense lesions, but also showed scattered foci of cystic and non-cystic encephalomalacia with diffuse parenchymal atrophy, especially in the bilateral frontal lobes, hippocampi, basal ganglia and brainstem. These findings were consistent with sequela of ANE.

After her acute hospitalization, she was admitted for an additional month of inpatient rehabilitation, where she made significant functional gains. By the time of her discharge from rehab, she had fully emerged from her disorder of consciousness, was able to walk household distances with

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hand-hold assist, communicate verbally, and had resumed eating a regular diet. Her nasogastric tube was removed. However, she has continued to struggle with delayed cognitive processing speed, difficulty with problem solving, impaired vision, and plantarflexor spasticity.

Discussion

Acute necrotizing encephalopathy (ANE) is a rare, fulminant form of encephalopathy associated with viral infections, most commonly influenza, and is characterized by multifocal symmetric brain lesions.[1–4] This case describes a previously healthy 6-year-old female who developed severe ANE in the setting of an influenza A infection, progressing to respiratory failure, prolonged encephalopathy, and significant neurologic sequelae. The characteristic MRI findings of bilateral involvement of the thalami, brainstem, and cerebellum, in conjunction with an elevated CSF protein and absence of pleocytosis, strongly support the diagnosis based on recent consensus guidelines.[2,4] While genetic predisposition has been described, with *RANBP2* variants implicated in familial and recurrent cases, genetic testing was not performed in this patient.[5,6] Her ANE severity score of 5 placed her in a moderate-to-high risk category for long-term neurological impairment, though additional studies are needed to further study this prognostic metric. In contrast, her EEG, although diffusely slow, demonstrated presence of spindles, which may portend a relatively favorable prognosis.[7] Modest sample sizes in all studies of ANE limit generalizability of prognostic tools.

The treatment approach in this case followed a multimodal strategy, including antiviral therapy, high-dose corticosteroids, intravenous immunoglobulin (IVIg), and supportive critical care revolving around neuroprotection. Although no standardized treatment protocol for ANE exists, immunomodulatory therapy is commonly employed based on the presumed role of cytokine dysregulation in disease pathogenesis.[2,7,8] Indeed, no randomized trials have been performed for this rare disease, but treatments in published case reports and case series revolve around similar immunotherapies and supportive measures.

Despite aggressive interventions, her prolonged disorder of consciousness and persistent hypertonicity highlight the considerable and potentially devastating impact of ANE. Follow-up MRI revealed evolving encephalomalacia and atrophy, particularly affecting the frontal lobes, hippocampi, and basal ganglia, structures critical for cognitive and motor function, although structure-function correlation is challenging. Nevertheless, these findings may correlate with her residual deficits in processing speed, problem-solving, vision, and motor control.

This case ultimately underscores the potential severity of influenza-associated ANE and highlights the importance of early recognition and aggressive supportive care. The patient's significant functional gains following intensive rehabilitation emphasize the role of neurorehabilitation in optimizing long-term outcomes. However, the persistence of cognitive and motor impairments illustrates the possibility of lasting disease burden, reinforcing the need for close multidisciplinary follow-up. Given that ANE seems to disproportionately affect children who have not received annual influenza vaccination, this case also serves as a reminder of the critical role of influenza prevention in mitigating severe neurological complications.[9,10] Finally, as there have been anecdotal reports of increased numbers of influenza-associated encephalopathy and ANE across the United States from the last two influenza seasons (2023-24 and 2024-25), this case represents a key contribution in disseminating contemporary ANE management strategies.[10]

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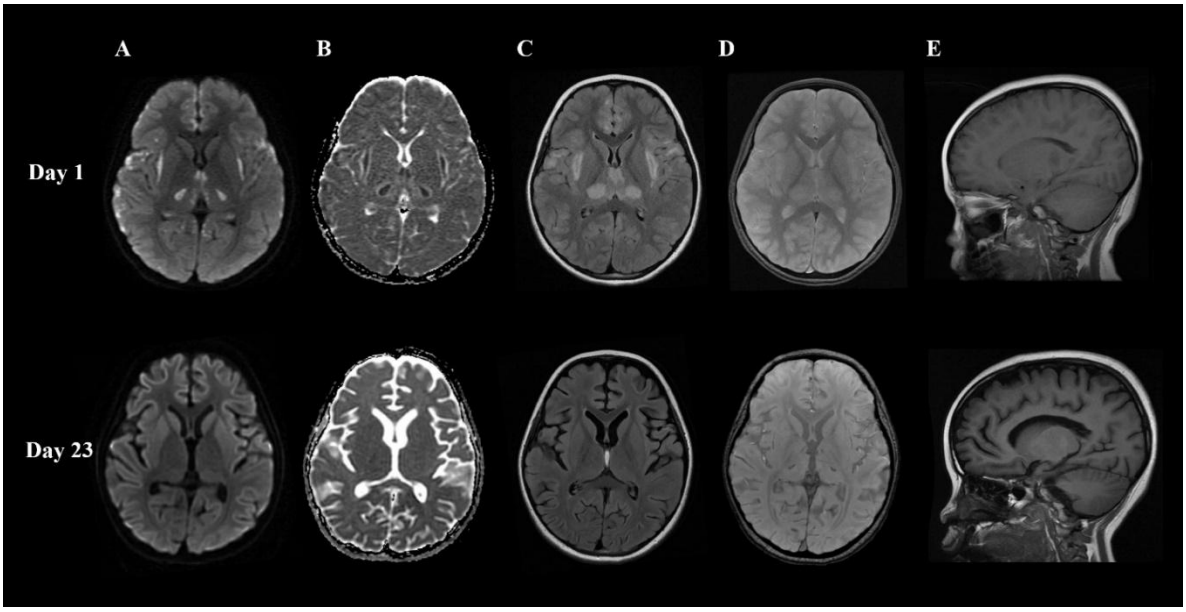

Figure 1. Brain MRI on days 1 and 23 of hospitalization. Panel A shows diffusion-weighted imaging (DWI), Panel B shows apparent diffusion coefficient (ADC), Panel C shows axial T2 FLAIR, Panel D shows susceptibility-weighted imaging (SWI), and Panel E shows sagittal T1. On day 1, neuroimaging is notable for multiple foci of restricted diffusion and T2 FLAIR signal abnormality seen most prominently in the bilateral insula, hippocampi, thalami, mamillary bodies, ventral pons, periaqueductal grey mater, medulla, and cerebellar vermis. Day 23 MRI shows resolution of diffusion restriction and T2 FLAIR hyperintensities but demonstrates encephalomalacia and cortical atrophy.

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