neurocritical care society Neurocrit Care (2010) 13:396–406
DOI 10.1007/s12028-010-9436-0

PRACTICAL PEARL

H1N1 Encephalitis with Malignant Edema and Review of Neurologic Complications from Influenza

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Published online: 2 September 2010

Abstract
Background Influenza virus infection of the respiratory tract is associated with a range of neurologic complications. The emergence of 2009 pandemic influenza A (H1N1) virus has been linked to neurological complications, including encephalopathy and encephalitis.
Methods Case report and literature review.
Results We reviewed case management of a 20-year old Hispanic male who developed febrile upper respiratory tract signs and symptoms followed by a confusional state. He had rapid neurologic decline and his clinical course was complicated by refractory seizures and malignant brain edema. He was managed with oseltamavir and peramavir, corticosteroids, intravenous gamma globulin treatment, anticonvulsants, intracranial pressure management with external ventricular drain placement, hyperosmolar therapy, sedation, and mechanical ventilation. Reverse transcriptase polymerase chain reaction analysis of nasal secretions confirmed 2009 H1N1 virus infection; cerebrospinal fluid (CSF) was negative for 2009 H1N1 viral RNA. Follow-up imaging demonstrated improvement in brain edema but restricted diffusion in the basal ganglia. We provide a review of the clinical spectrum of neurologic complications of seasonal influenza and 2009 H1N1, and current approaches towards managing these complications.
Conclusions 2009 H1N1-associated acute encephalitis and encephalopathy appear to be variable in severity, including a subset of patients with a malignant clinical course complicated by high morbidity and mortality. Since the H1N1 influenza virus has not been detected in the CSF or brain tissue in patients with this diagnosis, the emerging view is that the host immune response plays a key role in pathogenesis.

Keywords Encephalitis · Influenza · Encephalitis lethargica · Von Economo's Encephalopathy · Swine flu · H1n1 influenza · Influenza A

Abbreviations

ADEM	Acute disseminated encephalomyelitis
ANE	Acute necrotizing encephalopathy
ARDS	Acute respiratory distress syndrome
EL	Encephalitis lethargica
GBS	Guillain–Barre syndrome
IAE	Influenza-associated encephalopathy or encephalitis
PRES	Posterior reversible encephalopathy syndrome
SIRS	Systemic inflammatory response syndrome

Introduction

The current pandemic of 2009 influenza A (H1N1) (2009 H1N1) virus has presented challenges for clinicians

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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worldwide. Neurologic complications of seasonal influenza are likely under-recognized by neurologists and the frequency of acute or post-infectious neurologic complications with 2009 H1N1 virus infection is unknown. It is worth noting the historical relationship between H1N1 and neurology. Following the 1918–1919 H1N1 pandemic, an increase was observed in encephalitis lethargica cases [1].

What have neurologists learned about complications of 2009 H1N1 virus infections worldwide? We present a case report of 2009 H1N1-associated encephalopathy and review neurologic complications associated with seasonal influenza and 2009 H1N1 virus infection.

Methods

The Kaiser Permanente inpatient neurosurgery service maintains ongoing institutional review board approval for a prospective database registry for clinical research purposes. We identified a case of acute encephalopathy associated with 2009 H1N1 virus infection of the upper respiratory tract referred from an outside Kaiser community hospital for management. We conducted a detailed review of the electronic medical records.

We also conducted a literature review using PubMed. MESH search terms included influenza, encephalitis, encephalopathy, H1N1, acute necrotizing encephalopathy, and meningitis.

Case Description

A previously healthy 20-year old male college student had 5 days of non-productive cough, rhinorrhea, myalgias, and fever but no headaches or neck stiffness. On the 6th illness day, he presented to the emergency department of a community hospital with lethargy and confusion. He was electively intubated for airway protection. His chest X-ray (CXR) was normal. Routine admission laboratory tests including hepatic transaminases were within normal range. A non-contrast head computed tomography (CT) did not reveal any abnormalities (Fig. 1, top row), and he underwent lumbar puncture. Cerebrospinal fluid (CSF) analysis showed 53 WBC/μl with 91% lymphocytes, 6 RBC/μl, protein 113 mg/dl, and glucose 59 mg/dl. He was diagnosed with meningoencephalitis and started on vancomycin, ceftriaxone, acyclovir, and oseltamivir (150 mg twice daily per nasogastric tube). On the morning of the third-day of hospitalization, he experienced tonic-clonic seizures and remained comatose with extensor posturing afterwards. Repeat head CT (Fig. 1, bottom row) demonstrated diffuse brain edema and effaced basal cisterns. He received fosphenytoin, mannitol, and propofol. The treating physicians contacted the neuro-intensive care unit at Kaiser Sacramento for additional assistance.

He was emergently transferred to the Kaiser Permanente Sacramento neuro-intensive care facility (NICU). On arrival, his initial examination demonstrated a Glasgow Coma Scale of 3 (E1V1M1). His repeat CXR did not demonstrate

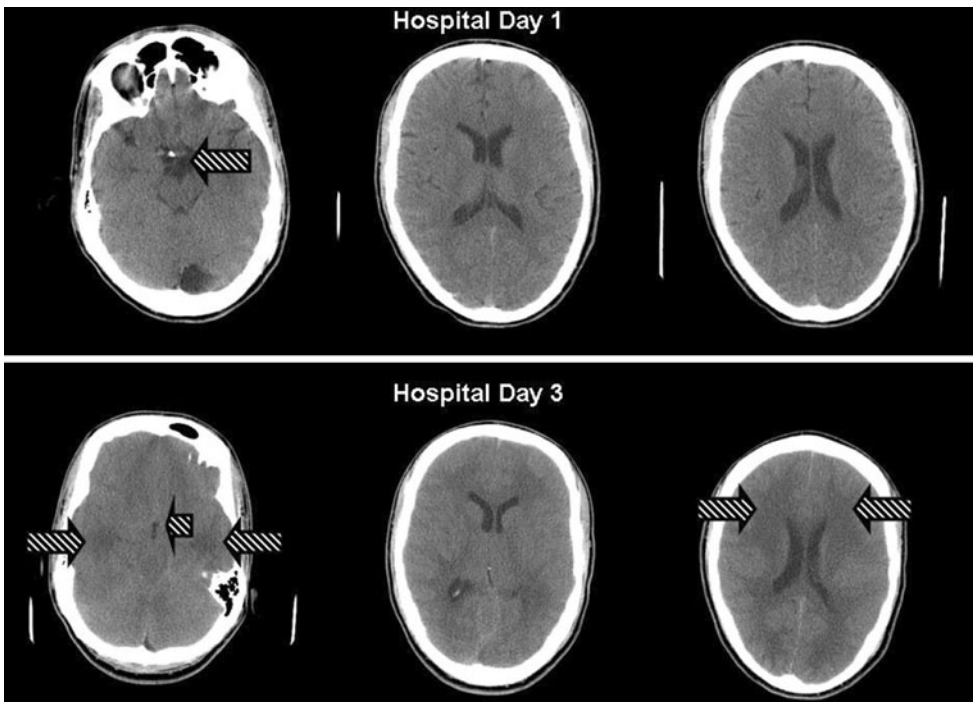

Fig. 1 CT brain imaging demonstrates rapid development of brain edema. The *top row* displays CT images from admission and the *bottom row* displays CT images 2 days later. The *arrow* on the *top row* (*left*) illustrates open basal cisterns. On the *bottom row*, the *small arrow* points to effacement of basal cisterns (*left*) and subcortical brain edema (*larger arrows*, *bottom row*, *left* and *right*). This subcortical edema is confirmed on MR imaging (Fig. 2)

any infiltrates or signs of acute respiratory distress syndrome (ARDS). An external ventricular drain was placed by the neurosurgeon at the bedside. He reported that the CSF pressure noted at the time of initial catheter placement was elevated. The first recorded intracranial pressure (ICP) was 10 mm Hg, and this reading was taken after the expected loss of CSF during the procedure. On the second day of NICU hospitalization, his Glasgow Coma Scale (GCS) score was 4 (E1V1M2) and average ICP was 7 mm Hg. Throughout the remainder of the hospitalization, the recorded ICP remained below 20 mm Hg. Initial ICP was maintained with external ventricular drainage at 0 cm relative to the external auditory canal and a midazolam infusion (5 mg/h). Electroencephalogram (EEG) monitoring demonstrated diffuse, severe slowing in the delta range and no electrographic seizures. On hospital day 3, MRI of the brain was obtained (see Fig. 2). He received 20 days of dual neuraminidase inhibitor treatment (oseltamivir 150 mg twice daily per nasogastric tube, peramavir 600 mg IV daily); intravenous gamma globulin (1 gm/kg × 2 days); dexamethasone (10 mg IV load, 6 mg IV every 6 h with taper over 4 weeks); ICP monitoring and management; ventilator support; and anticonvulsants (fosphenytoin, levetiracetam). His weekly Glasgow scale scores showed delayed improvement (3, E1V1M1, admission): 5 (E2V1M2, week 1), 5 (E2V1M2, week 2), 5 (E2V1M2, week 3), 9 (E3V2M4, week 4). The midazolam infusion was discontinued on hospital day 4, after clinical observation and EEG confirmation that he was not having electrographic seizures. Thereafter he received intermittent doses of lorazepam as needed for sedation while on the ventilator. Over 3 weeks, neuroimaging demonstrated improvement in his brain edema with restoration of his basal cisterns, and the external ventricular drain was successfully weaned and removed. More rapid weaning of his external ventricular drain was not attempted due to severe neurologic impairments with GCS less than eight and radiographic appearance of diffuse brain edema and effaced basal cisterns.

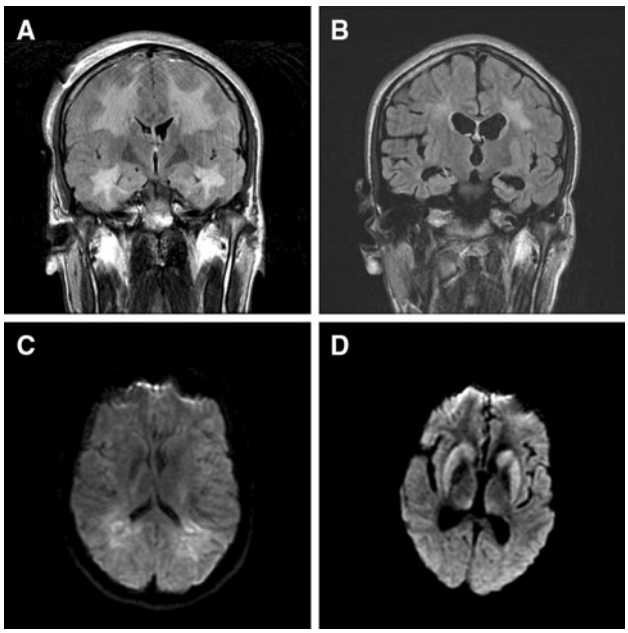

Fig. 2 Magnetic resonance imaging was done at the time of patient transfer **a**, **c** to the neuro-intensive care center and at 1 month of treatment **b**, **d** with influenza-specific antiviral therapy, corticosteroids, and intravenous gamma globulin therapy. **a** Coronal FLAIR image shows diffuse brain edema with sulcal effacement and symmetric hyperintensities selectively affecting the white matter and sparing cortex and subcortical nuclei such as basal ganglia and thalami. **b** Coronal FLAIR image at 1 month shows resolution of sulcal effacement, marked reduction in white matter hyperintensity, and relative brain atrophy (20 year old patient). **c** Diffusion-weighted imaging on admission showed some increased signal in the periventricular zones that were also bright on T2 and FLAIR sequences consistent with T2 shine-through. **d** Diffusion-weighted imaging at 1 month revealed hyperintensity in the caudate and putamen with corresponding decreased signal in ADC map and lack of hyperintensities on T2 and FLAIR sequences (see Fig 1b)

His NICU course was complicated by ventilator-associated *Klebsiella pneumoniae* and spontaneous pneumomediastinum on day 6 of intensive care. Chest CT demonstrated subcutaneous emphysema, mediastinal emphysema, bilateral lower lobe atelectasis, and no pulmonary interstitial emphysema, or pneumothorax. He did not develop adult respiratory distress syndrome or suffer periods of hypoxemia. RT-PCR of an admission nasopharyngeal swab was positive for 2009 H1N1 virus at the California Department of Public Health Virology Laboratory. RT-PCR analysis of CSF samples was negative for influenza A and B viruses, herpes virus type 1, 2, and 6, varicella, enterovirus, and Epstein Barr virus. Nasopharyngeal samples were negative for enterovirus and mycoplasma PCR. Bacterial and viral cultures of CSF were negative. Test results from clinical specimens (blood, endotracheal aspirate, serum, and CSF) sent to the California Encephalitis Project did not reveal an alternative cause. Follow-up MRI brain imaging (Fig. 2b, d) was repeated at 1 month. After 6 weeks, he transitioned to acute rehabilitation, and 1 month later returned home. Because he had improved upper extremity use without recovery in his legs, the physiatry staff performed spine MR imaging and no specific cause was identified.

At the time of this case report, the patient has returned home with his family. He is talking and interacting with his family normally. He has not returned to college. His gastromy tube has been removed. He has generalized rigidity without tremor or dyskinesia. He is ambulatory but requires a walker due to reduced endurance and leg weakness.

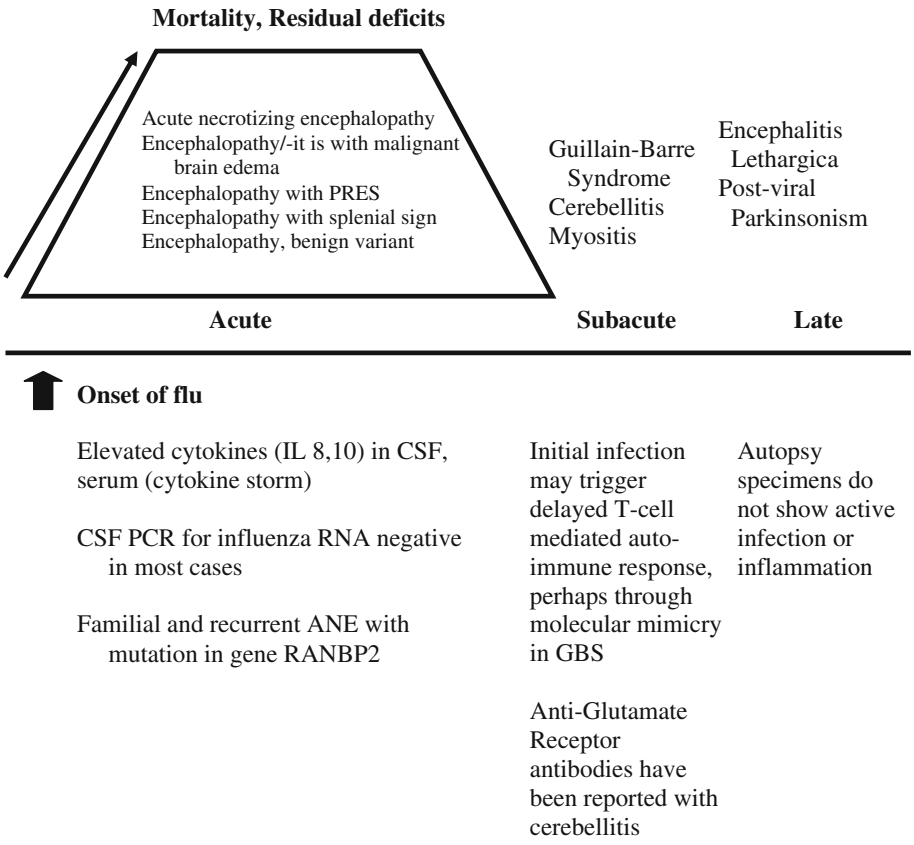

Fig. 3 Neurologic complications of influenza

Discussion

We present a case of a patient with acute encephalitis associated with febrile upper respiratory tract illness due to 2009 H1N1 complicated by seizures and malignant cerebral edema. Few adult cases of 2009 H1N1 influenza-associated acute encephalitis or encephalopathy have been reported to date. Descriptions of 2009 H1N1-associated neurologic complications are limited to case reports and small case series, and have been more commonly reported among young children. Given the current influenza pandemic, we provide an overview of neurologic complications associated with seasonal influenza and H1N1 (Fig. 3) and review clinical management and rationale.

Update on Pathogenesis of Influenza-Associated CNS Disease

Influenza virus infections can cause human respiratory disease and have been associated with a variety of central nervous system disorders [2]. Influenza virus has been rarely detected in CSF of patients that developed acute encephalitis/encephalopathy [3–5]. The systemic inflammatory response syndrome (SIRS) to influenza virus infection of the upper respiratory tract is hypothesized to play a prominent role in the more severe stages leading to cytokine dysregulation ("cytokine storm") in Influenza-associated encephalopathy or encephalitis (IAE) patients [6]. Elevated cytokines in serum and CSF have been reported in patients with seasonal influenza-associated encephalopathy [4, 7–10].

Elevated CSF to plasma ratios suggest activation of cytokine production within the CNS may have occurred along with the respiratory tract and systemic cytokines [7, 11, 12]. Microglia and astrocytes are capable of producing cytokines in the CNS [13, 14]. It is known that influenza virus infects and replicates at the nasopharyngeal epithelium leading to extensive damage during infection. Below the mucosa, the free nerve endings of the olfactory nerves may also become infected. As seen with Herpes simplex viruses, some postulate that influenza virus could penetrate and replicate at the olfactory mucosa and the free nerve endings with resultant axonal transport of virions to the olfactory bulbs, to the olfactory tract, and finally to the brain [15]. There is some literature to support this mechanism when one looks at H5N1, or avian influenza, where mice inoculated intranasally with H5N1 developed CNS lesions in the pons, medulla oblongata, and cerebellar nuclei. Astrocytes and glial cells were positive for viral antigen but viral replication ceased before 7 days [16, 17].

Table 1 Neurologic complications associated with influenza

Syndrome	Medical	Neurologic	Imaging	Lab	Treatment	Outcome
Encephalopathy, benign pattern	Fever, influenza-like illness symptoms	Encephalopathy, seizures	Negative CT, MRI	CSF benign, CSF influenza RT-PCR negative; diagnosis is by influenza testing of acute respiratory specimens	Oseltamivir, anticonvulsants	Rapid improvement; favorable
Encephalopathy, splenial sign	Fever, influenza-like illness symptoms	Encephalopathy, seizures	Reversible T2 signal and restricted diffusion in splenium of corpus callosum	CSF benign, CSF influenza RT-PCR negative; diagnosis is by influenza testing of acute respiratory specimens	Oseltamivir, anticonvulsants	Subacute recovery (weeks); favorable
Encephalopathy, PRES pattern*	Fever, influenza–like illness symptoms	Rapid, global neurologic decline	Increased FLAIR and T2 signal in centrum semiovale, more prominent posteriorly;vascular caliber changes have been reported	CSF with non-specific changes; CSF influenza RT-PCR negative; diagnosis is by influenza testing of acute respiratory specimens	Oseltamivir; ICP management; anticonvulsants; steroids, plasmapheresis, and IVIG have been reported	Variable
Encephalopathy, ANE pattern*	Fever, influenza symptoms	Rapid, global neurologic decline	Low density in thalami on CT; Increased FLAIR and T2 signal in thalami, midbrain, pons, cerebellum, and centrum semiovale	Lumbar puncture often contraindicated; influenza RT-PCR of CSF and brain negative; diagnosis is by influenza testing of acute respiratory specimens	Oseltamavir, ICP control, anticonvulsants, steroids, mannitol, hypertonic saline	High frequency of chronic morbidity and mortality
Encephalopathy with malignant brain edema*	Fever, influenza-like illness symptoms	Rapid neurologic decline	Diffuse brain edema, effacement of basal cisterns	Lumbar puncture contraindicated once edema develops; influenza RT-PCR of CSF and brain negative; diagnosis is by influenza testing of acute respiratory specimens	Oseltamavir, ICP control, anticonvulsants, corticosteroids, IVIG	High rates of morbidity and mortality
Post-infectious GBS	History of influenza-like illness symptoms	Weakness and areflexia	N/A	CSF with elevated protein without elevated WBC; serological diagnosis reported using paired acute and convalescent sera	IVIG, plasmapheresis, supportive care	Variable
Influenza-associated myositis	Influenza-like illness; severe muscle pain; weakness may be present	Muscles are tender; patients may walk on toes or with stiff legs; reflexes are preserved; (myocarditis can also develop)	N/A	Elevated creatine phosphokinase	Supportive care; alkalinized intravenous fluids if renal function is compromised (rare); fasciotomy if compartment syndrome present (rare)	Favorable
Post-infectious cerebellitis	History of influenza-like illness symptoms precede neurologic symptoms	Ataxia, personality changes	FLAIR and T2 changes in cerebellum; brainstem compression, tonsillar descent, and hydrocephalus indicate malignant subtype	CSF with non-specific changes; antibodies to glutamate receptor have been reported	Plasmapheresis and IVIg reported; in fulminant cases, consider posterior fossa decompression and EVD placement	Favorable unless malignant features are present

Table 1 continued

Syndrome	Medical	Neurologic	Imaging	Lab	Treatment	Outcome
Encephalitis lethargica	History of influenza-like illness symptoms; remote	Somnolent/ophthalmoplegic encephalitis; a subset manifested extrapyramidal symptoms	Loss of neurons in midbrain, subthalamus, and hypothalamus	CSF lymphocytic pleocytosis and variable protein elevation;archived tissue does not demonstrate influenza virus	Supportive	Chronic condition with considerable morbidity and 20% mortality
Post-viral parkinsonism	History of influenza-like symptoms; remote	Parkinsonism	Depigmentation of the substantia nigra and locus ceruleus, fibrillary changes and gliosis in the substantia nigra, oculomotor nucleus, and adjacent nuclei	N/A	Variable response to dopamine agonists and L-Dopa	Chronic condition

* Sometimes classified as ADEM [18]

Further study is needed to elucidate the pathogenesis of CNS disease complicating influenza A infection.

Neurologic Syndromes Associated with Influenza

Neurologic symptoms associated with influenza can arise at different intervals after the initial influenza illness (Fig. 3, Table 1). When assessing patients clinically, it is important to determine if the patient has active or recent symptoms (within days) of influenza or if the neurologic symptoms have appeared in a subacute manner. We will first discuss neurologic complications in the setting of recent influenza virus infection and then proceed to complications that present in a delayed manner

Influenza-Associated Encephalopathy

The development of a confusional state in the setting of influenza illness symptoms and fever raises the possibility of influenza-associated encephalitis or encephalopathy. The degree of encephalopathy varies from a confusional state to obtundation. It is important to recognize that a small portion of cases can rapidly deteriorate to coma and subsequent brain death due to diffuse, malignant cerebral edema. Focal and generalized seizures often occur and can be present with either mild or severe cases. The presence of fever and altered mental state should prompt clinicians to pursue CSF analysis unless neuroimaging or laboratory studies reveal a contraindication. Influenza illness may include upper respiratory symptoms, pneumonia, or diarrhea (more commonly in young children with seasonal influenza). A thorough medical assessment to exclude other causes such as sepsis, metabolic or toxic disorders, structural CNS diseases, and other CNS infections is warranted.

We define encephalitis by the presence of inflammation in the CSF or demonstration of viral infection in brain biopsy or autopsy specimens. We define encephalopathy when CSF is acellular and brain biopsy or autopsy specimens have failed to demonstrate viral infection. In some cases, this distinction is arbitrary and the case has borderline CSF pleocytosis or CSF analysis was not performed due to malignant brain edema. A consistent observation is that patients with seasonal influenza-associated encephalopathy rarely ever have evidence of influenza viral RNA in CSF based on RT-PCR analysis of CSF. Furthermore, there is no evidence of seasonal influenza virus infection of brain specimens. In one case series, only one out of 18 patients with acute seasonal influenza-associated encephalitis had influenza viral RNA detected [5].

Terminology for post-infectious encephalitis can be confusing. For example, the International Pediatric Multiple

Sclerosis study group [18] listed ten terms that have been used to describe acute disseminated encephalomyelitis (ADEM). Some terms focus on the triggering event, such as post-infectious encephalomyelitis; others on pathologic or pathophysiologic features such as acute demyelinating encephalomyelitis or hyperergic encephalomyelitis. These authors also classify acute hemorrhagic leukoencephalitis, acute necrotizing hemorrhagic leucoencephalitis (also known as acute necrotizing encephalitis, (ANE)), and acute hemorrhagic encephalomyelitis as hyperacute forms of ADEM. These diagnostic terms are of great historical interest. They generally preceded modern neuroimaging and relied more on the clinical and pathologic details. The study group also lumps a diversity of neuroimaging findings under the diagnosis of ADEM including: ring-enhancing lesions; diffuse and multi-focal regions of T2 hyperintensity with and without associated hemorrhage; multi-focal lesions with associated mass effect (tumefactive lesions); and images with symmetric, bithalamic edema. While we prefer one term (ADEM) rather than ten terms to describe post-infectious encephalitis, we are concerned that the pathophysiology and outcome of a process leading to the formation of ring-enhancing lesions (demyelinating, for example, acute demyelinating encephalomyelitis) must be radically different than that causing bithalamic edema (necrotizing, for example, ANE).

In reality, IAE presents along a spectrum ranging from milder cases with normal neuroimaging to more malignant cases with abnormal neuroimaging and less favorable outcomes. For the sake of discussion and literature review, we present a simplified classification scheme based on clinical and imaging findings.

The IAE benign variant can present with fever, confusional state, and seizures but neuroimaging with CT brain or MRI brain does not demonstrate any acute abnormalities. CSF analysis is within normal limits or has borderline findings. RT-PCR testing for 2009 H1N1 influenza viral RNA is positive in upper respiratory secretions but negative when CSF is tested [19–21]. These patients typically recover within 1 week, and most cases have received oseltamavir and anticonvulsants. The initial reports of pediatric cases of 2009 H1N1 encephalopathy in the US were not severe [19]. Similarly, other reported adult cases of 2009 H1N1 IAE without ARDS have not been severe with complete recovery [20, 21]. A more recent pediatric case series of 2009 H1N1 IAE reported that 2/4 patients had imaging abnormalities and neurologic sequelae [22], so the treating physicians need to be aware that full recovery is not a certainty.

The IAE with splenial sign presents with acute febrile respiratory illness and additional neurologic symptoms with a characteristic MRI abnormality. We found case reports associated with seasonal influenza but not with H1N1. It has been reported in children, but rarely in adults [23–28]. Encephalopathy is always present and can be severe. Seizures are often present. MRI imaging demonstrates increased T2 and FLAIR signal and restricted diffusion in the splenium of the corpus callosum. This finding is reversible. The MRI finding is not specific and has been reported with other infections, high-altitude brain edema, and certain metabolic states such as hypernatremia [29]. CSF analysis is unremarkable. These patients have been treated with oseltamavir and anticonvulsants, and typically recover within 1 month.

The IAE with posterior reversible leucoencephalopathy syndrome (PRES) presents as moderate to severe febrile encephalopathy. This subtype has been reported with seasonal influenza but not specifically with H1N1. The MRI imaging appears radiographically identical to PRES caused by more typical causes such as pregnancy or malignant hypertension [30, 31]. Vascular caliber changes have been observed in these cases; this is non-specific and can be related to infectious vasculitis or PRES. Given the diverse causes of PRES including malignant hypertension, pregnancy, metabolic disorders, and certain medications such as chemotherapeutics and immunosuppressants; it is often difficult to distinguish the pathophysiology of IAE in this clinical setting. Therapy is focused upon antiviral treatment, corticosteroid administration, and supportive care.

IAE with malignant brain edema is one of the most challenging subtypes to diagnose and treat. Both seasonal influenza and H1N1 can be complicated by severe forms of acute encephalopathy and malignant brain edema [32–35]. Survival in some cases has been achieved with aggressive neuro-intensive case management with other therapies, including administration of antivirals, corticosteroids, immunoglobulin (2 gm/kg in adult patients), hyperosmolar therapy, plasmapheresis, and hypothermia in some cases. One of the goals of treatment is to reduce viral expression with early antiviral treatment and thereby to reduce stimulation of the host inflammatory response.

Our case presentation illustrates the rapid time course for this complication (see Fig. 1) and neurocritical care treatment approaches. Because of diffuse brain edema, a broad treatment approach using hyperosmolar therapy, intubation, fever control, and sedation were important. To the best of our knowledge, this is the only case description of IAE in which an external ventricular drain was utilized, probably because it is difficult to place a catheter into the small, compressed ventricles of patients with diffuse brain edema associated with influenza.

Another adult case of H1N1 encephalitis has been reported with radiographic findings similar to ours. Fugate et al. [35] described an adult with H1N1 influenza-associated acute hemorrhagic leukoencephalitis. Like our patient, their case also showed confluent areas of increased T2

signal in the periventricular white matter and centrum semiovale. Because of the additional finding of microhemorrhages demonstrated on gradient echo MRI sequences, they diagnosed acute hemorrhagic leukoencephalitis or Hurst disease. Their patient also had restricted diffusion in the basal ganglia (see Fig. 2). Because their patient had severe adult respiratory distress syndrome (ARDS) with oxygen saturation readings in the range of 70–80%, the authors attributed the basal ganglia findings to hypoxic brain injury. Our patient did not have advanced pulmonary disease, hypoxia, or hypotension.

Care should be taken to distinguish IAE with malignant edema from Reyes' syndrome in which patients may present with lethargy, confusion, seizures, or coma accompanied by brain edema. Reyes' syndrome most commonly occurs in children but has been reported in adults following influenza and aspirin ingestion [36]. It can be distinguished based on the accompanying hepatic abnormalities, hyperammonemia, and hypoglycemia. Caution should be taken with any neurosurgical procedures in Reyes' syndrome due to increased risk of perioperative bleeding.

Influenza-Associated Acute Necrotizing Encephalopathy

One of the most devastating complications of seasonal and pandemic influenza is ANE [37–39]. Patients develop rapid neurologic deterioration to coma. Seizures are often present. Initial brain CT may show decreased density in the thalami, and MRI of brain demonstrates the characteristic bilateral thalami lesions. This finding may be initially mistaken for ischemic strokes (top-of-basilar syndrome) or venous infarction secondary to thrombosed internal cerebral veins, vein of Galen, or straight sinus. It is interesting that there have been case reports for recurrent ANE and also familial ANE. This suggests that there may be a genetic susceptibility and a gene associated with familial seasonal influenza ANE cases has been reported (nuclear pore gene, RANBP2; [40]).

This condition is often fatal or accompanied by permanent neurologic sequelae in surviving cases. It is intriguing that the neuroanatomical changes found in the thalami, midbrain, and cerebellum on neuroimaging correlated with the clinical symptoms reported for encephalitis lethargica, specifically "sleeping sickness", ophthalmoparesis, quadriparesis, and delayed parkinsonism (see below). It is conceivable that survivors with less fulminant involvement could manifest a clinical syndrome with symptoms and signs that localize to brainstem structures. A pediatric case of 2009 H1N1-associated ANE with bilateral thalamic imaging findings without associated malignant brain edema has been published [41], but detailed clinical follow-up was not reported.

Post-Infectious Neurologic Complications of Influenza

During the subacute period, additional classic neurologic syndromes associated with influenza have been described.

Post-influenzal cerebellitis is quite uncommon and has been reported rarely in adults [42–44]. This syndrome was diagnosed in a 31-year old woman who developed ataxia, dysarthria, and truncal titubation 1 month after influenza B virus infection, with neurologic symptoms that resolved gradually after an additional month. CT and MRI brain imaging were unrevealing. CSF studies detected evidence of the persistence of the NP gene of influenza B virus in the CSF from samples taken 7 and 9 weeks after the onset of initial influenza illness. A 25-year old woman gradually developed gait and speech problems after influenza A illness that was treated with oseltamavir. CSF showed pleocytosis. The cerebellar cortex had increased T2 signal which resolved over an 80 day period. She received pulse intravenous corticosteroid therapy. Her symptoms resolved [42]. Plasmapheresis [45] and IVIG [46] have also been used for this condition. Some cases of cerebellitis following viral and mycoplasma illness have developed fulminant cerebellar swelling with secondary brainstem compression, obstructive hydrocephalus, with fatal outcome [47]. Interventions with posterior fossa decompression and external ventricular drain placement may lead to a favorable outcome in a child with this severe condition. Antibodies to the glutamate receptor have been reported in patients with post-infectious influenza viral cerebellitis [44].

Guillain–Barre syndrome (GBS) is a subacute, immune-mediated disease predominantly affecting the peripheral nervous system. The diagnosis and treatment are well-known to most neurologists and this condition has been extensively described and reviewed. GBS has been rarely reported in association with seasonal influenza virus infection [48], but it should be noted that influenza testing is rarely pursued in GBS cases and may be unrevealing. Treatment for influenza-related GBS is identical to treatment for other GBS due to other associated causes. Monitoring for respiratory compromise due to neuromuscular weakness with timely respiratory support if needed is critical. Plasmapheresis or gammaglobulin treatments are also helpful. The precise pathophysiology is uncertain, but molecular mimicry of the infectious agent is presumed to stimulate autoimmune responses. This has been demonstrated to occur in *Campylobacter jejuni*-associated GBS [49].

Influenza-associated myositis has been reported with seasonal influenza [50] and H1N1 variant [51]. Myalgias

are a common symptom of influenza, but some patients develop frank weakness and have elevated serum levels of creatine phosphokinase (CPK). It is more common in children but has been seen in all age groups. The calf muscles are most suspectible, and patients may walk with a stiff gait or toe walk. Onset is usually within the first week of infection and spontaneous improvement typically occurs within 2 weeks in most cases. Rarely, severe cases can result in myoglobinuria-associated renal failure and compartment syndromes requiring fasciotomies. Influenza can also selectively attack specific muscle groups such as the heart (myocarditis). Muscle biopsy shows necrosis, regenerating fibers, and occasionally inflammation.

Post-viral Parkinsonism has been reported after an assortment of infections including influenza virus [52]. An outbreak of these cases was temporally noted following the Great Influenza (H1N1) pandemic of 1918–1919 [53]. Patients with this condition respond poorly to medical therapy, and it has an unfavorable prognosis.

Encephalitis lethargica is also known as Von Economo encephalitis and sleeping sickness [53]. A wave of such cases was reported following the 1918–1919 influenza A (H1N1) virus pandemic. The cardinal features of this condition are altered consciousness with prolonged somnolence and ophthalmoplegia. After intervals of months to years, survivors are at risk of developing parkinsonism. Pathological findings include nerve cell destruction primarily in the midbrain, subthalamus, and hypothalamus [53, 54]. Using modern laboratory techniques, formalin-preserved autopsy brain specimens of encephalitis lethargica cases analysed for influenza viral RNA were negative [54]. Scientists have proposed a "hit-and-run" model of early viral-mediated injury with late sequelae [54]. The neurologist Oliver Sacks [55] drew attention to this mysterious disorder and the discovery of L-dopa, in his book, Awakenings later converted to a feature-length movie. The delayed appearance of restricted diffusion in the basal ganglia in our patient and others [35] is concerning for this condition (Fig. 2). We do not know if this indicates that our patient with 2009 H1N1 is at risk of developing post-viral parkinsonism, but long-term clinical follow-up will be important. A delayed diffusion neuroimaging abnormality was also reported in the dentate nucleus of a patient with seasonal influenza encephalopathy/splenial sign [42].

Conclusion

We present a case of acute encephalitis associated with 2009 pandemic influenza A (H1N1) virus infection, complicated by malignant brain edema. The emerging hypothesis about acute neurologic complications of seasonal influenza is that the immune response triggered by influenza virus infection of the respiratory tract plays a prominent role in the pathogenesis of neurological manifestations. This hypothesis regarding the development of acute encephalopathy and brain edema is analogous to current theories about the role of the immune system and cytokines in the development of ARDS with 2009 H1N1 virus infection.

We have also provided an overview of the spectrum of acute and post-infectious neurologic complications reported in association with seasonal and pandemic influenza virus infection of the upper respiratory tract. Neurologists should be aware of the potential for a wide range of neurologic complications in association with the current 2009 H1N1 pandemic and seasonal influenza.

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