Acute Necrotizing Encephalitis in an Adult Patient with Novel Influenza A (H1N1) Infection

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Submission: October 03, 2015; Published: October 17, 2015

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Abstract

Neurologic complications of pandemic (H1N1) 2009 were first reported in children a case series of 4 pediatric patients in the United States in May 2009 [1]. Most subsequent reports were also of cases in children, because those <17 years of age appear most vulnerable [2], we are presenting a case of Encephalopathy in an adult young female with H1N1 influenza infection, with complete recovery, according to our records, this is the only case reported in the middle east.

Introduction

Influenza A (H1N1), which is also called human influenza virus with swine origin, has created a major worldwide health problem within a short time after its emergence [3]. This infection is often self-limited but sometimes can cause severe and fatal complications [4,5]. Involvement of the CNS in influenza virus infection is very rare, but serious manifestations like seizures, encephalitis, myelitis, Reye syndrome, and other neurologic disorders have been described previously in association with respiratory tract infection with seasonal influenza A or B viruses [6]. These findings indicate that, as with seasonal influenza, neurologic complications can occur with ongoing novel influenza A (H1N1) pandemic, but the frequency with which these occur is unknown. Encephalitis has been reported with novel H1N1 infection, mainly in children [7].

Other Neurologic manifestations of influenza are now known to include acute disseminated encephalomyelitis, Guillain-Barré syndrome, transverse myelitis, and acute necrotizing encephalopathy (ANE). Reports of ANE began surfacing from Japan during the influenza epidemics of the mid-and late 1990s [1]. According to studies from Japan, in the most severe cases of influenza-associated ANE, patients develop altered mental status with or without seizures and then rapidly progress to a comatose state within a mean of 24-72 hours from the onset of fever and upper respiratory symptoms [1,8,9]. Seizures are often resistant to antiepileptic medications. Death, which occurs in roughly 30% of cases, results largely from cardiorespiratory compromise or complications from mechanical ventilation [10].

Review of literature

H1N1 a localized necrotizing encephalopathy is being increasingly recognized CNS complication of H1N1& many case reports mainly from pediatric groups being published with few reported cases of adult patients with H1N1 encephalities in 2012 Elsevier Medical journal published an H1N1 influenza associated encephalitis [3] one case was Adult Patient with Novel H1N1 Infection Presented with Encephalitis, Rhabdomyolysis, Pneumonia and Polynuropathy [11]. Report of two rare complications of pandemic influenza A (H1N1) in November 2010 [12] which was aseptic meningitis and myocarditis. One reported case shows direct viral invasion of the CSF& detection of viral RNA & pleocytosis [10].

According to Joosten et al. [3] all patients were previously healthy, aged between 20 and 46 years, five were male and one was female. The most frequent initial clinical manifestations were influenza-like symptoms. Neurological symptoms included drowsiness, memory disturbance, disorientation, confusion, tremors and focal signs starting between 1 and 6 days after onset of illness. All patients had a laboratory-confirmed (nasopharyngeal swab) H1N1 virus infection. However, like in our patient, H1N1 RNA was not detected in CSF by RT-PCR. Other findings of CSF included elevated leukocyte counts and/or elevated protein levels. Neuroimaging findings were variable ranging from normal to cortical and subcortical lesions, like in our patient, to involvement of deep brain structures with or without brain edema. All patients were treated with Oseltamivir. Two patients received simultaneously treatment with corticosteroids. There was a complete recovery of neurologic manifestations in...
two patients; in three other patients mild to severe neurologic sequelae were noted.

Case Study

To our knowledge, encephalopathy associated with the novel H1N1 influenza strain was first reported in a case series of 4 pediatric patients in the United States in May 2009 [13,14]. All 4 patients had mild seizures and/or altered mental status and all recovered fully without any neurological sequelae at discharge. There has been only few cases reported of encephalopathy in a novel H1N1 infection in adult; we are reporting a similar case in adult previously healthy female.

A 40 years old Indian female previously healthy was admitted with 3 days of medium grade fever, non productive cough, shortness of breath and was diagnosed with Pneumonia, her Neurological examination was within normal, Laboratory studies revealed increased white blood cell count (17.4×10^9/L), Neutrophilia 85.5%, decreased lymphocytes 6.0, and elevated C-reactive protein of 15.8mg/dL. Serum electrolytes and renal and liver function tests were within normal limits. Her chest x ray shows bilateral scattered pneumonic patches; her H1N1 serology was positive, Tamiflu started on 3rd day of admission, Patient was shifted to intensive care unit and intubated Secondary to respiratory distress & hypoxia. She was sedated by continuous Dormicum infusion & Remifentanil, chest condition was getting better after three days from Tamiflu started.

Neurology service was consulted on day 6 as patient doesn’t regain consciousness after discontinuation of sedation. O/E ;pt was unconscious, not responding to verbal stimulation, in response to pain there is extension of lower limbs & moving upper limb, reflexes was brisk bilaterally, bilateral extensor planter Response. She had MRI, MRV, MRA done subsequently and showed Right frontal, right posterior parieto-occipital, left Temporo - parieto - occipital, extensive high cerebral and patchy left upper cerebral as well as right thalamic extending to upper right midbrain: hyper intensity suggesting micro bleeds and hemorrhagic components in T2, with some restriction in DWI, some T2 hyper intensities serpentine signals are seen filling the related suki and leptomeninges , likely representing meningeal exudates (Figure 1).

A lumbar puncture was performed. The CSF was clear colorless with normal Glucose & protein levels with no cells, further work-up to exclude other possible causes of encephalitis included (1) CSF polymerase chain reaction (PCR) for neurotropic virus was negative, including RT-PCR for 2009 H1N1 virus; (2) Cultures of blood, urine, tracheobronchial aspirate and CSF were negative; (3) Serology for mycoplasma pneumonia, Chlamydia, Rickettsia, hepatitis B and C, syphilis and HIV antibody was negative; (4) Testing for autoimmune disorders was within normal, absence of other causes and consistency of finding with other reported cases of the literature recommended the diagnosis of H1n1 encephalitis . MRI brain follow up done after 40 days shows: Mild increase in size and signal intensity abnormalities of the previously noted Rt frontal, Rt posterior parieto-occipital, left tempo-paario-Occipital, extensive Rt cerebellar and patchy upper cerebellar as well as Rt. thalamic extending to the upper right midbrain swollen edematous gyri and folia.

A course of IVIG was tried based on the reported cases of autoimmune nature of the disease, 2gm/Kg over 5 days, after which patient shows much improvement & regained consciousness 2 days after last dose of IVIG. Patient was is fully conscious, oriented to time, place & persons, indulges in family conversation, no focal neurological signs, apart from generalized weakness, preserved peripheral reflexes, bilateral equivocal planter responses, with no visual field defects, no signs of cranial nerves affection, preserved gag response, she was on nasogastric

Figure 1: Brain magnetic resonance images shows

- Patchy hypo-dense areas are seen scattered at the right cerebellar hemisphere , bilateral occipital and left tempro-parietal regions having cortical& subcortical locations with post contrast gyrual enhancement is noted
- Right thalamic non enhancing hypo dense area is also observed
- A small hyper-dense cortical focus is seeing at the left occipital region with insignificant post contrast enhancement.
- Concluded mild insignificant increase in the extent of the previously noted Viral H1N1 hemorrhagic necrotizing encephalitis and cerebellitis, with no resolution or new appearance of lesions or insults.
ND: Not Done; ILI: Influenza-Like Illness; CSF: Cerebrospinal Fluid; EEG: Electroencephalography.

been described [2,7,11-13]. The disease is associated with although cases associated with H1N1 and influenza B has also frequently associated with ANE is influenza A, H3N2 subtype, been associated with influenza A infection [3]. The strain most dysfunction. Approximately 18% of cases of ANE in Japan have been associated with fever and nonspecific symptoms, such as cough, emesis, and/or diarrhea, and quickly develop neurologic symptoms. Approximately 18% of cases of ANE in Japan have been associated with influenza A infection [3]. The strain most frequently associated with ANE is influenza A, H3N2 subtype, although cases associated with H1N1 and influenza B has also been described [2,7,11-13]. The disease is associated with significant morbidity and mortality, and survivors usually exhibit at least short-term neurologic sequelae [6]. In addition to antiviral therapies such as Oseltamivir, corticosteroids and intravenous immune globulin have been used to treat selected cases of ANE in Japan, with varying degrees of patient improvement [12]. Currently, there is no definitive treatment for ANE, and management of these patients’ centers upon supportive care for neurologic failure and treatment of increased intracranial pressure if present. Then they start monitoring some of Acute necrotizing Encephalitis in H1N1 adult infection.

Discussion

H1N1-associated encephalitis was defined by the Center of Disease Control and Prevention as altered mental status >24h, in patients with laboratory-confirmed H1N1 virus infection, within 5 days of influenza-like illness symptom onset plus two or more of the following: fever, focal neurological signs, CSF pleocytosis, EEG and/or abnormal neuroimaging indicative of encephalitis [1]. Our patient almost fulfilled all of these criteria. However it is noteworthy that neurological signs and symptoms were noted almost 20 days after the initial onset of respiratory illness when sedation was discontinued.

The clinical course of ANE is rapidly progressive; patients present with fever and nonspecific symptoms, such as cough, emesis, and/or diarrhea, and quickly develop neurologic dysfunction. Approximately 18% of cases of ANE in Japan have been associated with influenza A infection [3]. The majority of patients have been described with fever, cough, and fatigue, followed by headache, myalgia, and arthralgia [1]. The clinical presentation can range from mild to severe, with potential for neurologic sequelae [6]. In patients with laboratory-confirmed H1N1 virus infection, within 5 days of influenza-like illness symptom onset plus two or more of the following: fever, focal neurological signs, CSF pleocytosis, EEG and/or abnormal neuroimaging indicative of encephalitis [1]. Our patient almost fulfilled all of these criteria. However it is noteworthy that neurological signs and symptoms were noted almost 20 days after the initial onset of respiratory illness when sedation was discontinued.

Table 1(a,b): Clinicopathologic features of previously reported cases of H1N1 influenza-associated encephalopathy/encephalitis in adults.

| Author            | Sex  | Age (years) | Interval ILI-neurologic symptoms (days) | Neurologic Symptoms          | CSF                           |
|-------------------|------|-------------|---------------------------------------|------------------------------|-------------------------------|
| Fugate et al. (15)| Male | 40          | 30                                    | Confusion                    | No pleocytosis Elevated protein level RT-PCR H1N1-ND |
| Akins et al. (16) | Male | 20          | 6                                     | Confusion, seizures          | Pleocytosis Elevated protein level RT-PCR H1N1 negative |
| Chen et al. (17)  | Male | 40          | 2                                     | Tremors, clumsiness, right hemiplegia | Pleocytosis Elevated protein level RT-PCR H1N1 negative |
| Ito et al. (18)   | Male | 26          | Unknown                               | Memory disturbance, disorientation, drowsiness | Mild pleocytosis Normal protein level RT-PCR H1N1 negative |
| Gonzalez et al. (19)| Female | 46          | 3                                     | Confusion                    | No pleocytosis Normal protein level RT-PCR H1N1 negative |
| Tsai et al. (20)  | Male | 46          | 4                                     | Acute delirium               | No pleocytosis Normal protein level RT-PCR H1N1 negative |

| Author            | MRI                                           | EEG                                             | Antiviral Therapy | Prognosis            |
|-------------------|------------------------------------------------|-------------------------------------------------|-------------------|----------------------|
| Fugate et al. (15)| Subcortical lesions with hemorrhages and edema | Normal                                          | Oseltamivir       | Severe sequelae      |
| Akins et al. (16) | White matter lesions, diffuse edema           | Bilateral diffuse continuous slow 6 waves       | Oseltamivir 150mg/dia | Mild sequelae       |
| Chen et al. (17)  | Cortical and subcortical areas of the frontal-parietal lobe | Diffuse slowing of cortical activity | Oseltamivir       | Severe sequelae      |
| Ito et al. (18)   | Corpus callosum                               | Normal                                          | Oseltamivir 150mg/day | Complete recovery   |
| Gonzalez et al. (19)| Normal                                  | ND                                              | Oseltamivir       | Complete recovery   |
| Tsai et al. (20)  | White matter lesions                          | Bilateral diffuse continuous slow 6 waves       | Oseltamivir 150mg/dia | Mild weakness       |

ND: Not Done; ILI: Influenza-Like Illness; CSF: Cerebrospinal Fluid; EEG: Electroencephalography.

tubefeeding till she regain consciousness & started oral feeding. She was started on physical Rehab, but she was found to have bilateral drop foot with no back pain, preserved peripheral reflexes; on EMG showed: Generalized extensive axonal damage suggesting critical illness neuropathy, she was discharged after 35 days (Table 1) [15-20].

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