Adult Patient with Novel H1N1 Infection Presented with Encephalitis, Rhabdomyolysis, Pneumonia and Polyneuropathy

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ABSTRACT

Neurological complications of influenza are well known. Influenza A is commonly associated with neurological complications. Neurological complications especially encephalitis is described in the pediatric age group of patients with current pandemic novel H1N1 infection. We are describing a case of novel H1N1 infection presenting with multi-system involvement (encephalitis, bilateral pneumonia, severe rhabdomyolysis leading to renal failure and polyneuropathy) in adult patient.

Key words: Encephalitis, Novel H1N1, Polyneuropathy, Rhabdomyolysis

INTRODUCTION

Influenza is an acute, usually self limited, febrile illness caused by infection with influenza type A or B viruses that occur in outbreaks of varying severity almost every winter. Symptoms are primarily related to the respiratory system, but myositis, rhabdomyolysis, myoglobinuria, myocarditis, pericarditis, and central nervous system (CNS) involvement has been described with influenza virus infection.[1] 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.[2-5] These findings indicate that, as with seasonal influenza, neurologic complications can occur with on going 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.[6] There has been only one case report of encephalopathy associated with novel H1N1 infection in adult.[7]

We are describing a case of novel H1N1 infection presenting with multi-system involvement (bilateral pneumonia, severe rhabdomyolysis leading to renal failure and encephalitis) in adult patient

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CASE REPORT

A 27-year-old, male, immunocompetent patient presented with 5 days history of fever, running nose, dry cough, and sore throat. He also had complaint of breathless since 3 days. He had generalized tonic-clonic convulsion, altered sensorium and increasing breathlessness requiring ventilatory support after hospitalization. With this brief illness patient was transferred under our care with ventilatory support.

On examination, he was intubated and sedated, his limbs were swollen, pulse: 108/min, temperature: 37°C, and blood pressure was 138/84 mmHg. He was maintaining SpO_2 of 96% at 100% FiO_2 on controlled mode ventilation. CNS examination revealed sedated patient (receiving IV midazolam), pupils were normal size reacting to light, all deep tendon reflexes were absent, and there was generalized hypotonia. Auscultation revealed the presence of crepetitions in right infra scapular and infra-axillary regions of chest. Cardiovascular and abdominal system examination was unremarkable. Laboratory investigations on presentation to us showed hemoglobin: 14.42 gm%, total WBC counts: 1730 cells/cu.mm, platelet count: 1.25 lacs/cu.mm, serum bilirubin total: 1.2 mg%, direct: 0.5 mg%, indirect: 0.7 mg%, SGPT: 200 IU/L, SGOT:

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607 IU/L, alkaline phosphatase: 204 IU/L, LDH: 4491 IU/L, CPK total: 14,969 IU/L, CPK MB: 156 IU/L, urine myoglobin:>1000 ng/ml, total protein: 5.8 gm%, albumin: 3.0 gm%, globulin: 2.8 gm%, serum creatinine: 1.4 mg%, S. Na^+: 139 mmol/L, S.K^+: 5.0 mmol/L, C-reactive protein: 4.5 mg% (normal <1 mg%), serum procalcitonin: <0.5 ng/ml and arterial blood gas analysis was normal (on control mode ventilation with 100% FIO_2). His pharyngeal secretion was positive for H1N1 PCR testing at government referral laboratory for H1N1 testing. His X-ray chest showed right mid-zone consolidation, while ultrasonography of abdomen and 2D-echocardiography was normal.

He was treated with capsule Oseltamivir 75 mg 2 BID through ryles' tube, IV fluid, IV cefipime/tazobactum 1.125 gm q8h, IV midazolam, IV levetiracetam 500 mg q8h, other supportive treatment along with ventilatory support. Methyl prednisolone 40 mg q8h, sodium bicarbonate, IV levocarnitine, and IV pantoprazole was added to above regimen from next day. On second day he developed severe hypercapnia (PCO2: 146 mmHg), hypertension and tachycardia (no rhythm disturbances on ECG) and was treated with change in ventilatory settings, along with IV amioderone and nifedipine. From third day evening he started having continuous fever and worsening of serum creatinine (3.42 mg% which continue to worsen further up to 7.9 mg%). Despite this worsening creatinine level, he was maintaining urine output of 50-80 ml/h. His oseltamivir and antibiotic dosage were adjusted to creatinine clearance. Follow up investigations after 4 days showed hemoglobin: 14.6 gm%, total WBC counts: 14,100 cells/cu.mm, platelet count 2.2l acs/cu.mm, CRP: 4.81 mg%, serum procalcitonin: >10 ng/ml, CPK total: 3710 IU/L, S.K^+: 5.0 mmol/L, blood culture: sterile and X-ray chest (PA) showed right mid and lower zone and left lower zone consolidation, which showed worsening as compare to previous X-ray. His antibiotics were changed to Inj meropenem and fluconazole for suspected ventilator associated pneumonia. His blood cultures were sterile, but ET secretion grew *Klebisella pneumoniae*. (beta-lactamase resistance, KPC) resistant to meropenem. His antibiotics were changed to cefoperazone-sulbactum 3 gm IV BID and tygecycline 100 mg IV loading dose followed by 50 mg IV BID. After 48 hours of change in antibiotics his condition started improving and he was maintaining SPO_2 100% with FIO_2 40% on controlled mode ventilation. He continued to spike fever up to 40-40.5°C despite improvement in respiratory system. His repeated blood cultures were sterile. Injection caspofungin was started in place of fluconazole and continued antibiotics. His fever spikes reduced from third day onward and successfully weaned of in the next 3 days. His methyl prednisolone was tapered every fifth day (40 mg q8h for 5 days, q12h for 5 days, qd for 5 days followed by Tab prednisolone 20 mg for 5 days, 10 mg for 5 days and then stopped. His serum creatinine level plateau at 7.9 mg% before started improving. He also had brief hyperkalemia with (K+ level) between 5.5 and 6.5 mmol/L). His plain CT scan of brain was performed which was normal and CT thorax showed bilateral interstitial pneumonia with ground-glass opacities in right mid, lower and left lower zones [Figure 1].

He was subjected for non-contrast MRI brain and CSF examination once he was off the ventilatory support. MRI brain diffusion weighted images showed areas of restricted diffusion in the region of brain stem, posterior limb of internal capsule, periventricular region on both sides, deep while matter in both parietal region and splenium of corpus callosum and corresponding ADC MAP showed relative hypointense signals, all changes appear to be due to underlying Acute Demyelinating Encephalomyelitis (ADEM) [Figures 2 and 3]. CSF examination showed 5 cells/cu.mm, protein: 47.2 mg%, glucose: 93.7 mg% and gram stain results were negative. CSF PCR for novel H1N1 was not done. EEG was suggestive of encephalopathy with epileptic features. EMG-NCV was done on 14 day of hospitalization. EMG was normal, while NCV showed generalized predominantly pure motor, mixed axonal, and demyelinating polyneuropathy. His renal function started improving and became normal. CNS examination showed spontaneous eye opening, he try to follow verbal and painful stimuli with eye movement. He showed flexion movement of upper limb on painful stimuli, localizes pain in lower limb with generalized hypotonia and areflexia.

DISCUSSION

Neurological complications of seasonal influenza virus infection have been well described in Pediatric age group and young adults.[2,3,6,8,9] Neurological complications usually occur early in the course of disease[10,11] and include encephalopathy, encephalitis, seizures, Reye syndrome, and Guillain-Barre syndrome (GBS). Severity of complication ranging from mild and transient central nervous system alterations to severe forms associated with high mortality. The pathogenesis of influenza virus encephalitis is unclear. Whether the influenza virus invades the brain parenchyma is still a controversial issue. The viral RNA has been frequently detected in the CSF by RT-PCR.[12] However, recent reports have indicated that viral RNA is not detected in the CSF of most patients with influenza-associated encephalitis.[13,14] Findings of pathologic examination, including the lack of detectable viral antigen in brain

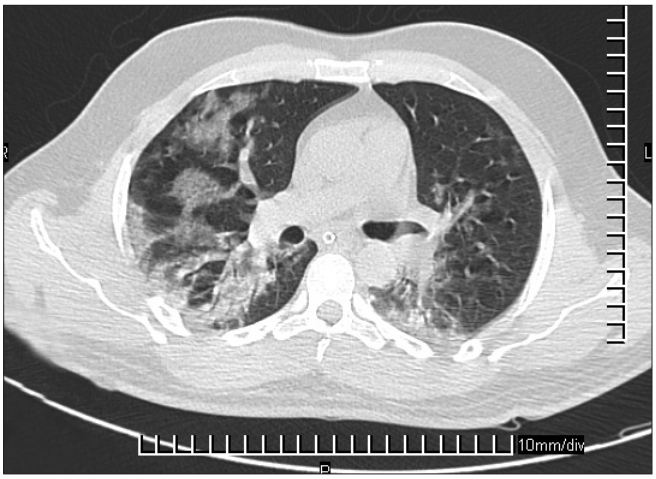

Figure 1: HRCT thorax: bilateral interstitial pneumonia with ground-glass opacities in right mid, lower, and left lower zone

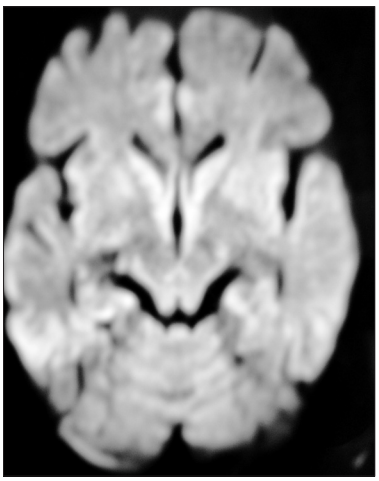

Figure 2: Diffusion-weighted images MRI brain: areas of restricted diffusion in the region of the brain stem

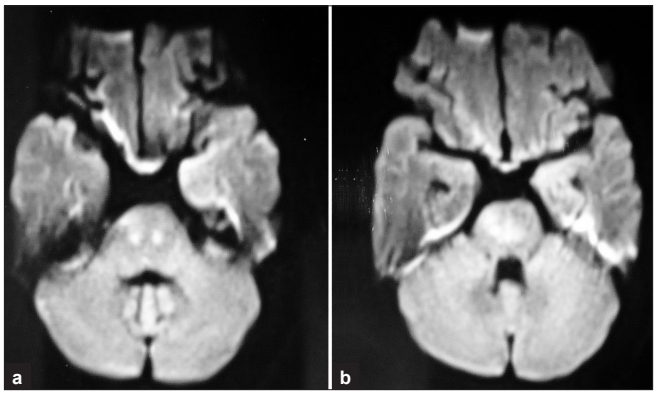

Figure 3 (a-b): Diffusion-weighted images MRI brain: areas of restricted diffusion in the region of posterior limb of internal capsule, periventricular region on both sides, deep while matter in both parietal region and splenium of corpus callosum

tissues, also have suggested that direct viral invasion and inflammation are unlikely to be the causes of this disease. It has been hypothesized that the respiratory tract infection triggers immune system cytokines that result, in rare instances, in an inflammatory process in the brain, which can lead to neurologic squeal or fatal outcomes.[6]

Neurological complications with Novel H1N1 pandemic reported so far are seen in the pediatric age group and many patients have recovered from H1N1 and develop neurological complications (polyneuropathy, transverse myelitis, encephalitis).

These patients had relatively mild neurological symptoms associated with the infection.[6] Our adult immunocompetent patient presented with initial symptoms suggestive of influenza-like illness of 5 days duration before he develops encephalitis. There is one report of novel H1N1 encephalopathy in adult female. Symptoms of encephalopathy were mild and recover without any specific treatment. However our patient developed episodes of seizures with loss of consciousness with ongoing acute phase of influenza virus infection, which was suggestive of CNS involvement by influenza virus. Our patient developed CNS involvement with acute lung injury, these timing of neurological involvement is consistent with available information in literature.[11] Patient had loss of consciousness with flaccid quadriplegia suggestive of extensive brain damage. The clinical findings of severe encephalitis were confirmed by evidence of extensive involvement of brain parenchyma on MRI brain examination performed after he recovered from acute lung injury. Methyl prednisolone 120 mg/day intravenously was used on presentation in our patient for the acute lung injury associated with viral pneumonia. His pulmonary pathology responded to oseltamivir and IV methyl prednisolone. He does have improvement in sensorium with persistent neuromuscular weakness. EMG-NCV examination showed generalized predominantly pure motor, mixed axonal and demyelinating polyneuropathy. Demyelinating polyneuropathy of GBS type has been well known after acute viral infections. It is difficult to differentiate critical care neuropathy from viral associated neuropathy with available investigations in our patient. GBS has been reported after influenza virus infection or after administration of influenza vaccine.[5] Glucocorticoids and plasmapherasis had been used in some patients with success. As patient developed secondary bacterial pulmonary infection glucocorticoids were not reintroduced later because of intermittent fever spikes.

Only one case report of rhabdomyolysis in Novel H1N1 patient so far in the literature, though it was well described with seasonal influenza. Our patient also had severe myositis, swollen limbs with rhabdomyolysis and myoglobinuria

(urinary myoglobin >1000 ng/ml) leading to renal failure on presentation. Myositis, rhabdomyolysis, and myoglobinuria are well known complication of influenza, although acute tubular necrosis and renal failure are not common.[11,15-19]

During hospitalization, he also developed tachycardia requiring use of IV amiodarone, for which we were not able to point out any immediate cause, raising suspicion of myocardial involvement by influenza virus. Nearly 9% of patients with proven influenza infection develop evidence of myocarditis.[20,21] Although the supportive investigations such as CPK MB, 2D echocardiography, and ECG were normal and we had not carried out any myocardial biopsy to confirm diagnosis of myocarditis. Generally, all these supportive investigations are inconclusive in most of the patients requiring myocardial biopsy for diagnosis.[22] As the myocardial involvement is patchy in nature it may some time be difficult to prove the presence of myocarditis even after doing biopsy.[22]

Severe inflammatory response generated by the body in response to influenza virus infection had led to more severe and extensive involvement of lung, muscle and brain. Our patient had multisystem involvement (pneumonia, encephalitis, neuropathy myositis, and possible myocarditis) from novel H1N1 influenza virus infection. Patient had incomplete recovery from all these insults with persistent neurologic dysfunction. This is probably first case report with multisystem involvement from novel H1N1 infection with significant post illness debility.

In conclusion, novel H1N1 infection can present with life-threatening multi-system involvement including encephalitis in adult patients.

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