Influenza A (H1N1) infection with acute kidney injury and hypoglossal nerve paralysis

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INTRODUCTION

Influenza is an acute febrile illness caused by infection with influenza type A or B viruses that occur almost every winter. Influenza A virus is the only virus that historically has caused pandemics. In April 2009, the influenza A (H1N1) virus caused the first influenza pandemic in over a 40-year period [1]. Influenza A (H1N1) is a member of the Orthomyxoviridae family and is an enveloped negative-strand RNA virus with six segments. It is spread mainly by inhalation of infectious droplets or airborne large droplet nuclei and possibly also by hand to mouth/nose transmission [2]. Although influenza is most often self-limited respiratory illness, severe complications followed by hospitalization and death can occur. The most common influenza-associated complications are pulmonary, especially pneumonia, but other organ systems can be affected too [1]. The incidence of acute kidney injury (AKI) was reported between 30% and 60% in influenza A (H1N1) syndrome [3,4]. Pulmonary injury and AKI were accused of increasing rate of mortality. Mortality rates of 16% and 54% have been reported among critically ill patients with H1N1 virus infection, respectively [5,6]. Involvement of central nervous system has been described in influenza A (H1N1) virus infections but the majority of serious neurological complications has been reported in children and likely represents the much higher viral infection attack rates in these groups [7]. Furthermore, the encephalopathy with or without seizures appears to be the most common major neurological association. Data of influenza A (H1N1) related focal neurological complications in adults hospitalized with influenza A (H1N1) are limited [8]. Here we report a case of patient with influenza A (H1N1) infection accompanied by severe multiorgan failure and focal neurological deficit.

ABSTRACT

The most common influenza A (H1N1)-associated complications are pulmonary, but other organ systems, such as kidneys and nervous system can be affected too. There are no sufficient data about the development of acute kidney injury (AKI) related to A (H1N1) infection. Neurological complications, especially encephalitis with or without seizures, have been documented among pediatric patients, but data of influenza A (H1N1) related focal neurological deficits in adults are scarce. Here we describe a previously fit 46-year-old male patient with influenza A (H1N1) infection presenting with multi-organ failure (acute respiratory distress syndrome and AKI) accompanied by muscular and unusual neurological complications. We found hypoglossal nerve paralysis and unilateral peroneal nerve paralysis in the course of the influenza A (H1N1) infection, but with no permanent neurological sequelae. Renal function was fully recovered one month after patient’s discharge.

Keywords: influenza A (H1N1), pulmonary complications, acute kidney injury, hypoglossal nerve paralysis

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**Case report**

A 46-year-old male patient was admitted to the Clinic for Infectious Diseases of the University Clinical Center Sarajevo (UCCS) in March 2014 with fever, cough, vomiting, myalgias and sore throat. Acute illness with fever started 5 days earlier. Patient had no history of major medical illness. On physical examination, his body temperature was 39°C, while conscious state, arterial blood pressure and pulse were normal. Chest auscultation revealed crackles at left bases. Laboratory examinations showed severe leukopenia (total white blood cell WBC counts 1.8x10^9/L), low platelet count (121x10^9/L), hypocalcemia (serum calcium 1.89 mmol/L) as well as elevated creatine phosphokinase (CPK 1.017 IU/L), aspartate amino transferase (AST 77 IU/L) and alanine amino transferase (ALT 45 IU/L) levels. He had normal kidney function at that point of time (serum creatinine level 93 μmol/L and CrCl 99.3 mL/min, according to the Cockcroft-Gault equation). Nasopharyngeal secretion was positive for H1N1 polymerase chain reaction (PCR) testing. A chest radiograph showed left mid and lower zone infiltrate. A diagnosis of viral influenza A (H1N1) pneumonia with secondary bacterial pneumonia was entertained and the patient was admitted in an isolated room. The initial treatment included oseltamivir phosphate 75 mg orally q12h, IV clarithromycin and IV fluid. Despite prompt treatment, the patient's respiratory status worsened with tachypnoea (respiratory rate 24/min), hypoxia (SO2 78%) accompanied by tachycardia (104 beats/min) and blood pressure lowering (90/60 mmHg). He required supplemental oxygen (face mask therapy O2 15-16 L/min) and his antibiotics were changed to IV ceftriaxone 2 g q24h and capsule doxycycline 100 mg q12h.

On the 3rd day of hospitalization, the patient was transferred to the Medical Intensive Care Unit (ICU) of the UCCS under care with ventilatory support for the reason of hypoxemic respiratory failure. However, he was maintaining only SO2 83% at 100% FiO2 on controlled mode ventilation. A chest radiograph showed left mid and lower zone infiltrate. A diagnosis of viral influenza A (H1N1) pneumonia with secondary bacterial pneumonia was entertained and the patient was admitted in an isolated room. The initial treatment included oseltamivir phosphate 75 mg orally q12h, IV clarithromycin and IV fluid. Despite prompt treatment, the patient's respiratory status worsened with tachypnoea (respiratory rate 24/min), hypoxia (SO2 78%) accompanied by tachycardia (104 beats/min) and blood pressure lowering (90/60 mmHg). He required supplemental oxygen (face mask therapy O2 15-16 L/min) and his antibiotics were changed to IV ceftriaxone 2 g q24h and capsule doxycycline 100 mg q12h.

On the 4th day of hospitalization, the patient was transferred to the Medical Intensive Care Unit (ICU) of the UCCS under care with ventilatory support for the reason of hypoxemic respiratory failure. However, he was maintaining only SO2 83% at 100% FiO2 on controlled mode ventilation. A chest radiograph revealed bilateral pulmonary infiltration (Figure 1A) which is typical for acute respiratory distress syndrome (ARDS). Laboratory tests showed worsening of leukopenia (WBC counts 1.28x10^9/L), increased levels of CRP (151.9 mg/L), hyperkalemia (serum potassium 6.2 mmol/L) and hypocalcemia (serum calcium 1.86 mmol/L). CPK, lactate dehydrogenase (LDH) and serum transaminase values were increasing too (CPK 2.042 IU/L, LDH 683 IU/L, AST 213 IU/L, ALT 98 IU/L). Although urine output was preserved (50-70 mL/h), his kidney function was worsening with an elevation of blood urea nitrogen (11.1 mmol/L) and serum creatinine (166 μmol/L) levels. Urine analysis showed aciduria (urine pH=5.0), sterile leukocyturia and proteinuria of 1.47 g/24h. Considering the most common bacterial pathogens in complicated post-influenza bacterial pneumonia, his antibiotics were changed again to IV vancomycin 1 g q12h and IV piperacillin/tazobactam 4.5 g q8h. Antiviral therapy with oseltamivir and supportive therapy was continued.

On the 5th day of hospitalization, serum creatinine level rose from baseline of 93 μmol/L to 297 μmol/L corresponding to the third stage of AKI, according to AKIN (Acute Kidney Injury Network) criteria [9]. Nevertheless, 48 hours after admission to the Medical ICU, his condition started improving and, in the next few days, he was maintaining SO2 100% with FiO2 40% on controlled mode ventilation. Body temperature, blood pressure, and pulse were normal with improving radiographic chest findings (patchy opacities only in the middle and lower lung zones on the 6th hospital day, Figure 1B).
Laboratory findings of WBC and platelet counts, as well as levels of CRP, serum potassium, and CPK tended to normalize. At the same time, the patient had normal urine output, but with further deterioration of renal function. However, antibiotic dose of IV vancomycin (initially 1 g q12h and later 1 g q24h) was not adjusted for worsening of renal function based on calculated CrCl. The peak level of serum creatinine (464 μmol/L) was registered on the 10th day of hospitalization. Antibiotic therapy with vancomycin and piperacillin/tazobactam was withdrawn on 7th and 10th day of admission, respectively, after results of blood, urine, and endotracheal aspirate culture remained negative. His renal function started to improve during the following few days and, on the 13th day of hospitalization, his serum creatinine level was 257 μmol/L. Although the 10th day was the first day without sedation in Medical ICU, 48 hours later patient was deeply unconscious (his Glasgow coma scale, GSC score was only 3). However, in the next few days, his neurological status has significantly improved. On the 16th day of hospitalization patient was finally extubated and was conscious but with some disorientation and confusion (GSC score 14). There was no further need for oxygen support and, for the reason of renal function evaluation, the patient was transferred to the Clinic of Nephrology of the UCCS (on the 20th day of admission with still elevated serum creatinine level of 233 μmol/L). In the meantime, neurological examination revealed dysphagia, dysarthria and walking abnormalities (a “slapping” gait with foot drop on the right side) accompanied with a weakness of the right foot. Also, his tongue deviated toward the left during tongue protrusion (Figure 2).

Non-contrast Computerized Tomography (CT) scan and magnetic resonance imaging of brain, as well as lumbosacral spine CT were normal. Electroencephalogram (EEG) showed non-specific activity (Theta waves) over the temporal lobes. Electromyoneurography (EMNG) confirmed unilateral peroneal nerve lesion. The diagnosis of the hypoglossal nerve (cranial nerve XII) and right peroneal nerve paralysis was established. Supportive therapy continued with added B-complex vitamin supplement and physical therapy exercises. Evaluation of kidney function showed proteinuria of 0.22 g/24h, aciduria, erythrocyturia (15 to 20 erythrocytes per high power field) and slightly lower values of serum creatinine level (202 μmol/L) with urinary creatinine to serum creatinine (UCr/SCr) ratio 25.2. During the next 10 days, the patient made incomplete recovery of renal function (serum creatinine level of 136 μmol/L) and was transferred to the Clinic for physical medicine and rehabilitation of the UCCS for ongoing physical therapy treatment. All neurological complications were resolved three months after initiation of physical therapy. One month after discharge patient showed complete kidney function recovery (serum creatinine level 97 μmol/L, CrCl 99.9 mL/min with no urine testing abnormalities)

**DISCUSSION**

Here we presented a patient with the early common mild signs and symptoms of viral influenza A (H1N1) who had later worsening of the clinical condition that led to multi-organ failure and unusual neurological complications.

Our patient was a 46-year-old immunocompetent male with no previous comorbid conditions. A recent study also confirmed that in comparison to those with the seasonal influenza adults hospitalized with influenza A (H1N1) are younger (median age 47 vs. 68 years) and less likely to have certain underlying medical conditions (chronic lung, renal, cardiovascular and metabolic diseases) [1]. Most symptoms of H1N1 infection are related to respiratory tract involvement. It is known that patients who require ICU admission have frequently experienced rapidly progressive, serious lower respiratory tract disease [10]. Our patient required mechanical ventilation for the reason of diffuse viral pneumonia complicated with bacterial coinfection, ARDS, and hypoxemic respiratory failure. Furthermore, he developed the most severe stage of AKI. Abdulkader and al. reported a significant association between the need for mechanical ventilation and AKI development (76% of the cases required mechanical ventilation) [5].

The frequency of myositis and rhabdomyolysis in H1N1 infection is unclear, but mild to moderate CPK elevation (1.000-5.000 IU/L) occurred in >60% of test-
ed patients [11]. Similarly, in the case of our patient, muscular complications did occur. Indeed, he had myalgia with abnormal muscle enzyme values (elevated serum CPK of >7 times the normal value) and aciduria. Elevated levels of serum transaminase and LDH, hyperkalaemia and hypocalcaemia were present too. The data in the literature suggest that rhabdomyolysis is one of the complications of viral infection which may be involved in AKI development and worsening [12]. However, the group of authors recently found no histopathological indicators of rhabdomyolysis such as pigmented cylinders in the renal tissue [13]. The same authors assumed that prerenal etiology was the main involved mechanism in AKI development since varying degrees of vacular degenerative tubular changes were present in all patients with A (H1N1) influenza. The prerenal factor with hemodynamic changes due to the multi-organ failure could be the main cause of AKI in our patient. Nevertheless, tubular injury due to the rhabdomyolysis should not be ruled out as a concomitant etiologic factor in AKI development, while the nephrotoxic effect of unadjusted dose of aminoglycoside antibiotics was likely involved in AKI progression as well as delayed recovery of renal function. The majority of neurological complications in influenza A (H1N1) has been reported in children and young adults. The encephalopathy-encephalitis and seizures or epileptic status appear to be the most common complications. Other complications are the stroke, acute disseminated encephalomyelitis and transverse myelitis [8]. In accordance with these findings, our patient also had encephalopathy with prolonged disturbance of consciousness once after sedation was withdrawn. However, he developed hypoglossal nerve paralysis and unilateral peroneal nerve paralysis later in the disease course. To our best knowledge, cranial nerve paralysis associated with peripheral nerve palsy due to the influenza A (H1N1) infection has not yet been reported. Finally, three months later, our patient had no permanent neurological sequelae. The good prognosis of some neurological complications with normal neuroimaging was also previously reported [7].

In conclusion, our case highlights the importance of recognizing significant pulmonary and extrapulmonary complications of influenza A (H1N1) infection. The early intervention and management can result in full recovery even in a case of the critically ill patient. As AKI is expected in patients with influenza A (H1N1) and multi-organ failure, early therapy with correct dose adjustment of potentially nephrotoxic drugs seems important for renal function outcome. Meticulous neurological evaluation with a long-term clinical and imaging follow-up of neurological complications is preferred in order to prevent permanent neurological sequelae.

**Declaration of interest**
The authors declare no conflict of interest.

**References**


