H3N2 INFLUENZA LUNG INFECTION AND ACUTE ENCEPHALOPATHY - CAN OSELTAMIVIR BE A COMMON SOLUTION?

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ABSTRACT Background: Influenza infection subtypes have emerged as a serious, fatal, but curable disease in many parts of the world for more than a decade. Though classically it involves the respiratory tract, there also can be extrapulmonary involvement of multiple organ systems in Influenza that can lead to death. Case Report: We report a 79-year-old male diagnosed with an H3N2 lung infection and treated with 5 days course of Oseltamivir. He later developed CNS complications. The possible causes of encephalopathy were ruled out after a thorough evaluation. Appropriate antibiotics and antiviral drugs were started, but the patient’s condition did not improve. Studies suggest various central nervous system complications, including encephalopathy that can occur secondary to Influenza virus infection. Influenza virus has been detected in CSF PCR, but the sensitivity is very low. The second course of Oseltamivir was started based on clinical judgement, after which the patient’s condition gradually improved. Oseltamivir was continued for 14 days. Conclusion: It is sometimes difficult to detect the causative organism in cases of CNS infection that can delay treatment. In such cases, empirical treatment with antibiotics and acyclovir or with antitubercular drugs is the usual treatment regime applied in most small hospital setups, after which the patient may or may not improve. Any history of a prior or recent attack of Influenza respiratory infection should not be missed by the clinicians and, if found so, CNS complications secondary to Influenza infections should be kept in mind. In such cases, it is imperative to add Oseltamivir to the treatment. The inclusion of an extended course of Oseltamivir can save lives in resource-limited setups.

KEYWORDS H3N2, Influenza, encephalopathy, CNS, Oseltamivir, extended course

Introduction

Influenza infection is endemic in many parts of the world. Since 2009, many outbreaks of Influenza have been reported. In recent years, cases of H3N2, apart from H1N1, are rising. Respiratory involvement is the classical presentation seen in Influenza, but other organs may be involved. Central nervous system (CNS) complications are well documented in H1N1 but rare in H3N2.

Case report

A 79-year-old male, unconscious for the past 30 minutes, was brought to the Emergency room of our hospital. His random blood sugar was 34 mg/dl. Hypoglycaemia was corrected, followed by a complete improvement in consciousness. There was also a history of hypoglycaemia 1 week back. Past history is suggestive of Hypertension, Diabetes Mellitus and Coronary artery disease (CAD) (Coronary artery bypass grafting; CABG done 6 years back). On examination, he was hemodynamically stable, with Bilateral crackles and rhonchi present, and Oxygen saturation (SpO2) was 80% at room air. The patient was

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We present a case of H3N2 infection that developed CNS complications during illness and recovered with an extended course of Oseltamivir.
immediately shifted to the intensive care unit for evaluation. Complete blood count showed a Total Leukocyte count of 11,200 cu/mm, Polymorphs 94%, Hemoglobin -8.2 gm%, Platelet- normal. HbA1c was 6.7%. Peripheral smear comments- Normocytic normochromic anemia, Total serum proteins-6.8 gm/dl, Albumin- 1.8 gm/dl, Globulin- 5 gm/dl, Albumin/globulin ratio- 0.4), Serum Urea- 39 mg/dl, serum creatinine- 1.51 mg/dl, serum sodium- 137 mmol/l, serum potassium- 2.9 mmol/l. Urine routine microscopy- normal, High-density lipoprotein-21.2 mg/dl, Cardiac markers- negative. We started our evaluation to search for any lung infection and causes that could independently cause hypoglycemia, like diabetic nephropathy. Throat swab came positive for H3N2 influenza infection. High-resolution computed tomography of the chest showed minimal bilateral pleural effusion and subpleural congestion in dependent parts of the upper and lower lobes of both lungs. Electrocardiogram and echocardiography; were done to assess the current cardiac status; showed sinus tachycardia with no fresh ST-T changes and showed mild global hypokinesia, left ventricular ejection fraction of 40%, aortic valve sclerosis, mild to moderate Aortic regurgitation, no Aortic stenosis, mild Mitral regurgitation respectively. An H3N2 positive lower respiratory infection diagnosis was made, and treatment was started with the tablet Oseltamivir and other supportive measures. The patient’s condition started improving as treatment began, but on the third day, the patient again became drowsy. Glasgow coma scale (GCS) was E4V2M5. Blood sugar was normal. There was hypoxia with oxygen saturation of 84%. ABG was done that was suggestive of high PaCO2. The patient was put on non-invasive ventilation. A repeated chest X-ray showed horizontal fissure effusion on the right side. This is a common finding because of underlying heart failure. [18] Injection Furosemide infusion was started, and the repeat chest X-ray was normal the next day. But despite the resolution of radiological findings, the patient was still in altered sensorium. Repeat ABG was normal. Cardiac, neurological, pulmonary status and electrolytes were reassessed. Serum electrolytes were normal. Bilateral plantar extensor with no neck stiffness. Deep tendon reflexes were normal. Bilateral pupils were normal size and reactive to light. CT Head suggested of gliosis in left frontal cortex due to old MCA infarct, diffuse periventricular white matter ischemic changes, senile brain atrophy. A clinical diagnosis of an acute encephalopathy, probably secondary to an infection, was made. CSF sample was collected for analysis, and empirical treatment was commenced, suspecting bacterial and/or viral cause; IV dexamethasone followed by IV Ampicillin, Ceftriaxone, IV Vancomycin and IV Ayclovir. CSF analysis was normal except total white blood cell count 20 cells/cumm CSF analysis was normal except total white blood cell count 20 cells/cumm. After 6 days of antiviral and antibiotics, no change in consciousness level was found. The second course of Tablet Oseltamivir was started with the possibility of encephalitis secondary to H3N2. The patient’s consciousness level was better the next day and improved after that. Oseltamivir was continued for an extended course of 14 days along with steroids. He was discharged in good health.

Discussion

H3N2 influenza virus is a type of Influenza type A virus. In a recent Andhra Pradesh, India study, neurological complications were reported in 2 out of 38 H3N2 positive patients.[1] In a study done by one of the current authors (Verma et al.), neurological complication was seen in 8 of 64 positive patients, of which 7 died.[2] Neurological complications in Influenza have been reported in children [3] and young adults. Neurological complications are more commonly associated with H1N1 than with H3N2. The most common complications are disorientation, and altered consciousness.[4] others include convulsions, myelitis, encephalopathy, meningitis, Guillaume Barre syndrome, and Reye syndrome. [5,6] Definitive diagnosis of CNS complications due to Influenza is difficult because of the lack of a uniform clinical picture, unavailability of a reliable test to detect Influenza virus in CSF,[7,8,9], and many comorbid factors etc. The true pathogenic mechanism of CSF complications in Influenza infection is still unknown. Few studies suggest high levels of cytokines like interleukin-6 and tumour necrosis factor-alpha in the CSF of affected patients. [10, 11] One of the studies suggests that blood-brain barrier permeability is increased in Influenza patients, facilitating virus access from the blood into the CSF.[12] Another mechanism is inflammation and infection of neurons. [13,14,15], Steininger et al. suggested that MRI may not be useful in acute Influenza encephalopathy but may show gross lesions in post-infectious encephalomyelitis patients.[4] We report this case as a general condition, and the consciousness continuously improved after reinitiating Oseltamivir. We don’t claim that it is a proven case of Influenza encephalitis. We added Oseltamivir as the patient’s condition was not improving. This case reporting highlights how the rational use of Oseltamivir in setups with limited resources can be used to save a life. Our decision to use Oseltamivir is also supported by the studies done by findings of Meijer et al. in which strong emphasis is given to the consideration of Influenza-associated CNS complications as a differential diagnosis in patients with unexplained CNS symptoms in patients presenting in Influenza season. Their study also found that negative PCR in CSF does not always rule out the diagnosis of Influenza-associated CNS complications. Therefore testing for PCR may not always be helpful. They also concluded that treatment regimes for such patients should include broad-spectrum antibiotics, Ayclovir, steroids, and Oseltamivir. However, a definitive treatment regime for treating the CNS complications of Influenza is still undefined.[16] Our case reporting also supports that Oseltamivir can be used for an extended duration in suspected clinical conditions. In a study by Asolami et al., Oseltamivir was used at 75 mg twice daily for the first 4 days. Then the dose was increased to 150 mg twice daily along with corticosteroids. Treatment was continued for 15 days, followed by a clinical improvement.[17]  

Limitation of case

MRI brain of the patient could not be done. CSF analysis for H3N2 PCR could not be done due to logistic issues. EEG could not be done.

Conclusion

Neurological complications in Influenza, though rare, do exist. Clinical suspicion of such a condition can save a life in cases with unexplained neurological signs. Unfortunately, testing methods are neither available in all hospital settings nor are they completely reliable. A definitive diagnostic criterion for Influenza-associated CNS complications is still lacking. Extended courses of Oseltamivir can improve the condition. More studies are required for a better understanding of the disease, diagnosing the problem, treatment and long-term prognosis of the infection.
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Conflict of Interest
There are no conflicts of interest to declare by any of the authors of this study.

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Abbreviations
1. CNS- Central nervous system
2. CAD- Coronary artery disease
3. CABG- Coronary artery bypass grafting
4. SpO2- Oxygen saturation
5. HbA1c- Glycosylated Hemoglobin
6. GCS- Glasgow coma scale
7. EVM- eye, verbal, motor
8. ABG- Arterial blood gas
9. CO2- carbon dioxide
10. CT- Computed tomography
11. MCA- Middle cerebral artery
12. CSF- Cerebrospinal fluid
13. MRI- Magnetic resonance imaging
14. PCR- Polymerase chain reaction
15. EEG- Electroencephalogram

References