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Case Report

Acute exacerbation of psychiatric symptoms during influenza treatment with oseltamivir in chronic schizophrenia

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Abstract

Influenza treatment and prophylaxis with oseltamivir are critically important in reducing the morbidity and mortality of patients in chronic psychiatric facilities. Abnormal behavior, delusions, perceptual disturbances, mania, and depression have all been reported as oseltamivir-related psychiatric side effects. We hereby report two chronic schizophrenia patients in Taiwan manifesting psychiatric instability who were being treated with oseltamivir for suspected influenza infection, and further discuss other potential contributing factors. The possibility that oseltamivir can cause psychotic or affective symptoms suggests that additional caution is necessary for its use in patients with an established psychiatric diagnosis.

Keywords: influenza; oseltamivir; psychiatric symptoms; schizophrenia

1. Introduction

Psychiatric patients hospitalized in a chronic ward setting are at a high risk for infectious diseases, especially those which are highly contagious such as influenza.[1] Infection control measures, as well as immediate treatment and appropriate prophylaxis with antiviral agents such as oseltamivir, are of paramount importance in chronic mental health facilities to prevent an influenza outbreak and to minimize morbidity and mortality of those infected.[2,3] We hereby report two cases of chronic schizophrenia patients in Taiwan manifesting acute exacerbation of psychiatric symptoms while being treated with oseltamivir for suspected influenza B virus infection, and further discuss the potential contributing factors and treatment recommendations.

2. Case reports

There were a total of 100 patients in this chronic psychiatric ward; 40 female patients lived on the first floor with four patients/room and 60 male patients lived on the second floor with five patients/room. These 100 patients shared the same public spaces such as the dining areas, recreational quarters, and exercise spaces, although each patient room was equipped with a toilet.

The two cases presented below lived in the same room for 4 days with an index case of influenza B infection confirmed by rapid test for influenza antigen. This index case was a 49-year-old single man with chronic schizophrenia and without a history of systemic disease. For purposes of clarity in disease course description, we designated the day on which both of our cases first experienced onset of fever as Day 1. Tracing

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back the illness history, the index case patient went on a 6-day home leave from Day −13 to Day −8, wherein he had spent time with a family member with upper respiratory infection symptoms. He returned to the psychiatric ward on Day −8 and lived with the two cases in the same room for 4 days from Day −8 to Day −5. The index case developed a fever and upper respiratory symptoms since Day −5 and was transferred to a single room. He later developed secondary pneumonia and was transferred to the intensive care unit with endotracheal intubation on Day 1.

Five days after the fever episode of the index case, both cases developed fever exceeding 38°C, headache, and prominent upper respiratory symptoms. Influenza B infection was strongly suspected in both cases, although the results of rapid tests for influenza antigens were negative. According to Taiwan Centers for Disease Control (CDC) regulations for treatment of influenza-like-illness, oseltamivir was prescribed for both cases due to the close contact history and also due to the history of diabetes mellitus in Case 1.

2.1. Case 1

Mr. Y, a 41-year-old single man, was diagnosed with schizophrenia at the age of 19 years, with presentations of auditory hallucinations with a voice commenting, persecutory delusion, violent behavior, and significant academic function deterioration. He had been a patient on our ward for 11 years, suffering psychotic symptoms which were controlled with clozapine 400 mg/d. Additionally, social withdrawal and affective flattening were prominent. The patient also had hypertension and type 2 diabetes mellitus under medication control with olmesartan 20 mg QD, metformin 500 mg QD, and glimepiride 2 mg BID.

On the 1st day of suspected influenza infection, with symptoms of fever, sore throat, rhinorrhea, headache, and muscle soreness, clozapine was decreased to 300 mg/d and further dropped to 150 mg/d on Day 3 to attenuate the sedative effect and prevent sialorrhea-related aspiration. Oseltamivir 75 mg BID for 5 days was prescribed beginning on Day 2. Thereafter, delusion with paranoid and grandiose content associated with agitation developed on Day 5. He became uncooperative in his compliance with treatment procedures, such as intravenous catheter insertion and quarantine in a single room, and required frequent physical restraints. Clozapine was then titrated up to 200 mg on Day 5, 250 mg on Day 6, and 300 mg on Day 7. Thereafter, his psychotic symptoms rapidly improved and disappeared on Day 9. His fever subsided on Day 4 and upper respiratory symptoms resolved completely on Day 14.

2.2. Case 2

Mr. L, a 71-year-old married man without chronic physical illness, was diagnosed with schizophrenia at the age of 40 years, with persecutory and religious delusions, auditory hallucinations, and violent behavior. He had been admitted for 7 years and psychotic symptoms were under control with quetiapine 200 mg/d without prominent negative symptoms.

His symptoms of fever, headache, sore throat, and rhinorrhea had developed on Day 1. On Day 2, the same oseltamivir regimen was prescribed and quetiapine was decreased to 100 mg/d to reduce its sedative effect. On Day 4, hypomanic symptoms with elevated mood, flight of idea, hypertalkativity, and hyperactivity disturbed Mr. L's infection control procedures. Quetiapine 200 mg/d was resumed on Day 7 and the hypomanic symptoms resolved on Day 10. Ultimately, his fever subsided on Day 5 and upper respiratory symptoms cleared on Day 15.

3. Discussion

Psychiatric patients hospitalized in chronic wards are highly susceptible to influenza infections that cause substantial morbidity and mortality.[4] Oseltamivir, a neuraminidase inhibitor, is extensively used in the treatment and prophylaxis of suspected influenza A and B virus infection.[5] Oseltamivir-related neuropsychiatric events of abnormal behaviors, delusions, and perceptual disturbances have been reported in Japan, the United States, and other countries.[6] Furthermore, there were case reports indicating that oseltamivir may induce mania[7] and depression.[8] This evidence primarily stemmed from case reports or postmarketing surveys among patients without previous psychiatric disorders. The possibility that oseltamivir could cause psychiatric symptoms requires its cautious use in patients with an established psychiatric disorder.

Oseltamivir has earlier been shown to affect neuron functioning and behavior in animals.[9,10] Specifically, oseltamivir may cause psychiatric side effects by influencing dopaminergic neurotransmission. First, oseltamivir may increase dopamine release from the presynaptic neurons. Significantly elevated levels of dopamine in the medial prefrontal cortex after intraperitoneal administration of oseltamivir has been reported in rats.[11] Second, oseltamivir may enhance agonist-induced dopamine D2 receptor activity. By inhibiting neuraminidases that are also sialidases, oseltamivir reduces the hydrolysis of sialic acid linkage to glycolipids. Subsequently, these sialoglycolipids boost the effect of increased D2 receptor activity by agonists. This mechanism has been implicated in an animal study linking oseltamivir with abnormal behavior.[12] Oseltamivir may assert a similar influence on the human nervous systems and cause prominent psychiatric symptoms. Further investigations by human experimental studies are indicated.

Delusions, hallucinations, and manic/hypomanic manifestations have also been related to influenza infection with or without encephalitis.[13–16] The possibility of influenza infection itself precipitating the psychiatric instability observed in our cases further complicated the treatment of influenza in chronic psychiatric patients. On the one hand, oseltamivir may potentially worsen psychiatric symptoms; on the other hand, possible influenza-induced exacerbations of psychiatric symptoms warrant oseltamivir treatment.

Decreasing the antipsychotic dosage during influenza treatment might also contribute to psychiatric instability.

Particularly, reducing clozapine dosage within a short period may cause withdrawal symptoms related to cholinergic crisis and manifest as agitation, abnormal movements, and worsening of psychotic symptoms.[17] This "rebound psychosis" was demonstrated to be related to the increased binding of endogenous dopamine to the D2 receptor after clozapine withdrawal.[18] Clozapine, quetiapine, olanzapine, zotepine, and risperidone have been associated with an increased risk of pneumonia in schizophrenia patients from a nested case−control study utilizing Taiwan's National Health Insurance Research Database.[19] This is one of the reasons we tapered down the antipsychotics. The other reasons were to prevent oversedation and aspiration related to extrapyramidal side effects or clozapine-induced sialorrhea.

The obvious emergence of psychotic and hypomanic symptoms in our chronically stable patients would have caused difficulty in the proper treatment of influenza and related physical symptoms without the aid of frequent physical restraints. Fortunately, the psychiatric symptoms remitted promptly in both patients after titrating up the antipsychotics close to the original daily dose.

In conclusion, to our knowledge, these are the first case reports addressing psychiatric instability during oseltamivir treatment among chronic psychiatric patients. Although influenza infection itself or the decrement of antipsychotics may also be contributing factors, this nevertheless highlights the need for vigilant use of oseltamivir in this specific population.

Currently, there are no standard guidelines regarding antipsychotic dosage adjustment when oseltamivir is used for chronic psychiatric patients. Our recommendation is that antipsychotics should be continued at the original dosage level during oseltamivir treatment to prevent psychiatric destabilization, which may sequentially impede the management of physical symptoms. If deterioration of the patients' physical condition is suspected to be related to antipsychotics, the dosage should be cautiously tapered down temporarily and resumed to the original dosage as soon as possible.

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