

Fabiola Méndez-Sánchez¹
Moisés Bolívar-Perálvarez¹
Francisco F. Rodríguez²
Juan A. Guisado-Macias¹

Oseltamivir- related psychiatric manifestations

¹Psychiatry Service of the Hospital Infanta Cristina
Badajoz

²Infectious Disease Unit of the Hospital Infanta Cristina
Badajoz

The importance effect on the population of the new virus Influenza A/H1N1 and the potential therapeutic with Oseltamivir. Clinical case. Patient of 62 years old, without history of interest, contracted Influenza A, that she undergoes a confusional syndrome responding to antipsychotics and with complete recovery after the episode. Conclusions. Establish the possible relationship between the various factors are influencing the onset confusional syndrome in a patient infected with Influenza A treated with Oseltamivir.

Key words:
Influenza A, Confusional syndrome, Oseltamivir

Actas Esp Psiquiatr 2012;40(1):46-8

Manifestaciones psiquiátricas relacionadas con oseltamivir

Destacar la afectación en la población del nuevo virus Influenza A/H1N1 y la posibilidad terapéutica con oseltamivir. Caso clínico. Paciente de 62 años, sin antecedentes de interés, que contrajo la Gripe A, sufre un Síndrome confusional, que responde a antipsicóticos y con recuperación completa tras el episodio. Conclusiones. Establecer la posible relación entre los diversos factores que influyen en la aparición de un síndrome confusional en un paciente infectado con la gripe A que recibe tratamiento con Oseltamivir.

Palabras clave:
Gripe A, Síndrome confusional, Oseltamivir

Correspondence:
Dra. Méndez
Avenida Ricardo Parapeto N° 80 1° E Badajoz CP: 06008.
E-mail: fmendezsanchez@yahoo.es

INTRODUCTION

The human H1N1 strain is a subtype of influenza A virus of influenza, belonging to the Orthomyxoviridae family. The H1N1 has mutated into different subtypes, such as swine flu, better called the "human flu," since it currently has not been isolated in animals. The importance of this virus is precisely how it affects the human being. It produces clinical pictures similar to seasonal flu. However, at other times, it causes severe pneumonias or even death, as has been occurring since the middle of March 2009, detecting 184 deaths in Europe and America due to the pandemic of said virus, with suspicion of 100 more unconfirmed deaths in Mexico.¹ The situation recorded by the WHO up to June 14 shows 29,669 confirmed cases of influenza caused by the new H1N1 virus strain and hundreds of deaths worldwide. Oseltamivir (Tamiflu®) is a neuroaminidase inhibitor used in the treatment and prophylaxis of patients with suspicion of infection due to Influenza A and B virus with typical flu symptoms at a dose of 75 mg/twice a day. It can cause a wide spectrum of side effects, among which neuropsychiatric ones stand out.²⁻⁴ We present the case of a female patient infected by the new A/H1N1 influenza virus who is being treated with Oseltamivir. The patient, after several days of hospitalization, developed a delusional or confusional syndrome, the second most prevalent psychiatric syndrome in the hospital setting (10 – 30%) following depressive disorders, requiring high doses of antipsychotics for its improvement.⁵

CASE DESCRIPTION

A 62-year-old woman was admitted to the Hospital Infanta Cristina of Badajoz due to being infected by the new A/H1N1 influenza virus.

As personal backgrounds, she was an ex-smoker of 10 cigarettes/day until a few years ago and has been diagnosed of COPD. She does not report any family backgrounds of interest.

The patient works as a Primary Care physician and caught the disease in a home visit. Three days later, she began with fever (38°C), dry cough, rhinorrhea and arthralgia. The following stood out in the physical examination: presence of the mildly erythematous oropharynx, and bilateral hypophonesis with rales in both lower fields in the pulmonary auscultation. The electrocardiogram showed a sinus rhythm with prominent P waves in leads II, III and aVF. The chest x-ray on admission showed mild increase of the bronchovascular network without infiltrates.

Treatment was initiated with oral oseltamivir, with the appearance of good initial response (disappearance of fever and muscle pains), up to five days later, and associated bronchodilator treatment (ipratropium bromide every 6 h, terbutaline and budesonide every 12h). Complementary tests were requested to verify infection by the new A/H1N1 influenza virus:

- Laboratory: hemoglobin 14.6 g/dl, Leukocytes 4300/mm³, platelets 141000/mm³.
- Coagulation: prothrombin activity, APTT and fibrinogen - normal.
- PCR: 9.4 mg/l.
- TSH normal.
- Baseline arterial blood gases: pH 7.48/pCO₂ 32/pO₂ 61/HCO₃ 24/ SatO₂ 92.4%
- Study of new A/H1N1 influenza virus positive in nasal smear and blood.
- Serology for C. Burnetii, M. pneumoniae and C. pneumophila negative.
- Normal Protein electrophoresis and IgA, IgG and IgM.
- Lymphocyte subpopulations: CD4 427/40%; CD8 134/13%.
- Chest X-ray (performed four days after hospitalization): no pulmonary infiltrates are detected nor other important images.

After being hospitalized for three days, in isolated regime, the patient began with a picture of disorientation and restlessness, that became a picture of psychomotor agitation, with behavior disorganization, recognition problems, verbose speech that was incoherent and with delusional content, that was fluctuating and that worsened in the afternoon, so that mechanical restraint was applied and a regime of 1 ampoule intramuscularly of levomepromazine and diazepam, 10 mg, were administered. This had to be repeated due to lack of response to the first administration. Given the situation of the patient, it was decided to establish a risperidone dosing guideline of 4 mg and tiapride 400 mg, divided into two administrations. In subsequent days, imaging tests were performed: magnetic resonance (MR), in which a discreet cortical-subcortical atrophy was observed with small hyperintense images in periventricular white matter of both hemispheres in relation to ischemic lesions – chronic degenerative; and single photon

emission computed tomography (SPECT), in which left frontal hypoperfusion and discreet heterogeneity of the global perfusion were observed.

During the ten days of hospital stay, the behavioral and thought alterations disappeared, with adequate speech and adaptation to the hospital and relational setting. Only some hypothymia, reactive to the picture suffered, needs to be mentioned. Entry into the home to assure her adaptation to her usual setting was allowed, with excellent response, so that she was discharged from hospital with risperidone 2 mg/24h, sertraline 50 mg/24h and diazepam 5 mg/24h.

DISCUSSION

The clinical manifestations of the A/H1N1 influenza virus are similar to any respiratory infection (fever, cough, myalgias, odinophagia, headaches, etc.). In some cases, it can cause disorientation, confusion and irritability². In 2006, in the United Kingdom, a study was conducted on the incidence of neuropsychiatric effects in patients infected by the virus regarding the general population belonging to the database *General Practice Research Database*. In 75% of the patients infected, a two-fold increased risk was found compared to the general population, above all hallucinations, panic attacks, decrease of awareness level and cognitive distortions.

The importance of the neuropsychiatric effects produced by Oseltamivir goes back to the period of 2004 – 2005 in which there was an increase in the incidence said side effects in the pediatric population, above all in Japan, where 60% of the patients who were under treatment with antivirals suffered them, regarding 30% in the USA and less than 1% in France and the United Kingdom.² The American FDA made a review and discovered a total of 129 cases (including 3 deaths due to said neuropsychiatric effects) in the period of 2005 – 2006, compared with 126 cases from the time that Oseltamivir was put on the market in 1999 until 2005. The reasons for these results are unknown since there was no increase in the incidence of the virus or changes in its characteristics and modifications in the manufacturing, doses or administration of Oseltamivir. In 2007, a *warning* appeared on suicidal behavior in the population group with ages ranging from 10 – 19 years.^{2,4,5}

The most frequent psychiatric manifestations are: behavior alterations, perceptual distortions and confusional syndrome. Cases of suicidal ideation, above all in young adults, have also been described.²⁻⁴

In the delirium, there are some factors facilitating its appearance (multiple conditions, previous cognitive impairment, sensory deficits or excesses, isolation, prolonged immobilization, etc). Those patients subjected to major surgical interventions, oncology and terminal patients,

patients with multiple medications and with hydroelectrolytic disorders having the greatest risk (precipitants).⁵ On the other hand, there are series of predisposing factors defined by Lipowski, such as elderly age and vulnerability of the children, due to the grade of neurobiological maturation, as well as personal, and the presence of any type of alteration or injury in the central nervous system (cerebrovascular accident, cranial traumatism, Parkinson's disease or drug addiction). The neuroimaging studies, in some cases, show alterations such as atrophy or cerebrovascular accidents on the cortical and subcortical level (above all frontal cortex and basal ganglia), however the existence of delirium without lesion is more common. In regards to the functional tests, something similar occurs in some cases. There is a decrease in blood flow of frontal and parietal predominance, there being, however, problems for the detection of global flow changes due to the low sensitivity of the SPECT.⁶

Considering that both the virus and Oseltamivir individually produce neuropsychiatric manifestations,^{2, 7} when both converge, we could consider that there is an increased risk of suffering them, as occurs in the case in the clinical note presented. Other factors have also played a part in this, such as the hospitalization, isolation, organic conditioners (COPD), delay in the initiation of the action of oseltamivir and the concomitant treatment with bronchodilators.^{5,8} In the literature, cases have been reported on transient delirium behavior 2-3 days after the onset of the infection and of the treatment with Oseltamivir, that improved with antipsychotics. These cases did not suffer neuropsychiatric sequels.² However, in our case, we stress a prolonged hospital stay, due to persistent paranoid symptoms once the infection was resolved,⁷ which finally improved

with antipsychotic treatment without residuality.

The purpose of the publication is to present the probable relation between the appearance of delirium and multiple factors, that exert a synergic effect on them, such as the virus infection, treatment with oseltamivir, hospitalization, isolation and alterations on the imaging tests, in a female patient with good premorbid functioning and without any background of interest, who recovered her baseline level.

REFERENCES

1. OMS. Alerta y respuesta ante epidemia y pandemia. Gripe A/ H1N1.
2. Toovey S. Assessment of Neuropsychiatric Adverse Events in Influenza Patients Treated with Oseltamivir. *Drug Safety*. 2008;31(12):1097-114.
3. Okumura A, Kubota T, Kato T. Oseltamivir and Delirious Behavior in Children With Influenza. *The Pediatric Infectious Disease Journal*. 2006;25(6):572.
4. Oseltamivir: neuropsychiatric disorders. *Revision Prescrire*. June 2007;27(284):435.
5. Matías González T, Joan de Pablo R, Valdés M. The clinical confusion about delirium. *Revista médica de Chile*. 2003;131:1051-60.
6. Alsop DC, Fearing MA, Johnson K, Sperling R, Fong TG, Inouye SK. The Role of Neuroimaging in Elucidating Delirium Pathophysiology. *The Journals of Gerontology*. 2006;61A(12):1287-93.
7. Kruker AT, Krause M. Oseltamivir – induced delirium. *Therapeutis Umschau. Revue thérapeutique*. 2010 Dec;67(12):613-5.
8. Jefferson TO, Demichell V, Pietranonj DI, Jones M, Rivetti D. Inhibidores de neuroaminidasa para la prevención y el tratamiento de la Influenza en adultos sanos. *Biblioteca Cochrane Plus*, 2008 Número 4.