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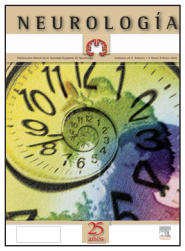

LETTERS TO THE EDITOR

The probable neurological spectrum of influenza A (H1N1)

El espectro neurológico probable de la influenza A (H1N1)

Dear Editor,

The world is confronting a new pandemic. First known as "swine flu", it quickly spread thanks to the phenomena linked to globalization: cross-border mobility, international travel, etc. Despite the initial attempts made by Mexico to halt the spread of the disease, the outbreak continued to grow and advance towards neighbouring countries and to the whole world in a matter of just a few days; tourists who had enjoyed their holidays returned home to their respective countries taking an invisible and unknown enemy with them: influenza A (H1N1).

The influenza virus belongs to the family of the Orthomyxoviridae, RNA viruses that are classified into four genera: A, B, C, and Thogota and Dhori (the last two are transmitted by ticks and rarely affect humans). In order to describe them, a nomenclature is used that includes the type (antigenic specificity of its nucleoprotein and the matrix protein), the host of origin, its geographical origin, the recording of the strain, and the year it was isolated. In the case of the A strain (H1N1), it tells us that it is of the Influenza A genus and presents the antigenic characteristics of haemagglutinin and neuraminidase. Haemagglutinin is a glycoprotein that acts as a receptor for sialic acid (N-acetyl-neuraminic acid) and induces penetration of the viral particles by means of membrane fusion; neuraminidase catalyzes the glycosidic bonds with sialic acid and facilitates the release of virions outside the infected cell.[1]

On June 11th, 2009, the World Health Organization raised the alert level to phase 6, indicating that we were facing a pandemic; at that time, more than 70 countries had reported 28,774 cases of influenza A (H1N1) and 144 deaths as a result of the disease.[2] Apparently, the first cases appeared between March and April, 2009, in Mexico and the United States. The virus was dispersed in the same way as seasonal influenza, namely through sneezing and coughing. It was also indicated that it might be acquired by touching one's nose or mouth with hands that had touched contaminated surfaces.[3]

In April, 2009, laboratory tests conducted at the CDC in Atlanta confirmed the first patient with influenza A (H1N1). On April 26th, 2009, the United States administration declared a public health emergency related to the new virus.

At the time this article was sent for review, Guatemala had reported 528 cases of influenza A (H1N1), the latest bulletin put out by the WHO reported 162,380 cases worldwide (60.5% of the cases were in America and 16.1% in Europe) with 1,154 deaths (87.3% in America and 3.6% in Europe).[4] Studies on the economic impact of the illness have yet to be carried out.

After an average incubation period of 5 days, the patient begins with a combination of headache, runny nose, sneezing, cough, muscle aches and achy joints, fever, vomiting, and diarrhoea. The intensity of the condition may vary depending on factors such as the age of the patient and their immune status. Mortality in the general population is low, amounting to 0.25%.

At the beginning of the pandemic, no neurological symptoms were reported, but in July, 2009, four children presented in Texas with initially unexplained seizures that were later attributed to influenza A (H1N1).[5] The first case was that of a 17-year-old patient with flu-like symptoms in whom influenza A (H1N1) was confirmed; hence, treatment with oseltamivir was initiated. Twenty-four hours later, he suffered generalized weakness (strength 12) and disorientation, normal CSF; the patient evolved favourably and was discharged on day 5. The second case was that of a 10-year old child who had gone to the Emergency Room after presenting a 3-minute, generalized tonic-clonic seizure (GTCS) after 4 days of fever, cough, general apathy and fatigue; in the hospital, he presented fever, weakness, and was disoriented. A few minutes later he suffered another GTCS lasting for 3 minutes and the diagnosis of influenza A (H1N1) was confirmed. At the Intensive Care Unit he presented a complex focal seizure that secondarily generalized and lasted for 30 40 min and remitted with lorazepam and phosphenytoin; the magnetic resonance scan of the brain was normal. Oseltamivir and rimantadine were added to treatment; his mental status returned to normal on the seventh day of hospitalization. The third patient was 7 years old and went to the hospital with a history of coughing, nasal congestion, fever, fatigue, and a GTCS lasting for 2 min; a diagnosis of influenza A (H1N1) was made at the time of admission. The EEG revealed non-specific focal activity; he was treated with oseltamivir and rimantadine. The patient was discharged on the third day in good condition and with levetirazetam as anticonvulsant

therapy. The fourth patient, an 11-year old male, consulted due to fever and vomiting; he also presented fatigue, headache, abdominal pain and ataxia. Shortly after being admitted, he suffered a seizure characterized by upgaze deviation; a diagnosis of influenza A (H1N1) was made and treatment with oseltamivir and rimantadine was then initiated, to which cephotaxime and aciclovir were added. During his hospitalization, the patient presented visual hallucinations, slowed response to verbal orders, slowness of speech. He returned to a normal state on the fourth day of hospitalization.

At our clinic, we have had the chance to evaluate a 42-year old male patient with painful, sensitive neuropathy that started up one week after finishing treatment with oseltamivir indicated for influenza A (H1N1). The flu began with cold-like symptoms accompanied by fever, nasal secretion, arthralgia, and headache; within 12 h, the patient's temperature had gone to 41 and 42°C, persisting for 48 h despite the use of antipyretics. Twenty-four hours after onset, the patient was extremely apathetic and began with vomiting and diarrhoea. Treatment was initiated on the second day. The diagnosis had been formulated at the onset of symptoms, given the presence of a similar clinical picture in the same home and in light of the laboratory diagnosis. On the fifth day after starting treatment with oseltamivir, his condition had resolved, albeit the fatigue and slowed thinking persisted. One week later, neuropathy appeared characterized by paresthesia on the tips of the third and fourth fingers of both hands, pain in both wrists, and a slight loss of strength, which resolved over the course of 2 weeks with the sole treatment of support splints and non-steroidal anti-inflammatory drugs, prescribed due to the patient's desire not to use any other type of medication.

A second case of probable sequela of influenza A (H1N1) presented in a 10-year old child that evolved with the clinical symptoms of the illness and resolved without the need for treatment. In the following days, the child displayed emotional lability, as well as some somatic manifestations of anxiety, patterns that had not been observed previously. His condition began to improve during the second week after introducing treatment with a serotonin uptake inhibitor.

Flu viruses have any number of neurological manifestations; hence, infections due to influenza A (H1N1) may be grounds for seeking medical care. In the four cases reported, we find focal seizures and GTCS, ataxia, altered state of consciousness, headache, and decreased muscle strength.

At the present time, we have only individual, anecdotal reports of cases of patients infected with influenza A (H1N1) who have manifested neurological problems; nevertheless, we must consider that, just like any other flu virus, there may be a broad spectrum of manifestations. We must also add that the medications used to treat it are not free from neuropsychiatric side effects. At the UNED we have evaluated a 12-year old patient suffering from anxiety and depression after recovering from influenza A (H1N1).

The neurological manifestation most commonly associated with flu are febrile seizures;[6] these patients generally suffer more than one seizure and their general condition resolves without neurological sequelae in most cases. However, there may be an increased risk that the patient might subsequently suffer non-febrile seizures.

Up to 5% of all cases of encephalitis are caused by the flu virus and this is described as being rare or uncommonly diagnosed[7]. Morishima et al. studied 148 cases in an outbreak of encephalitis/encephalopathy that took place in the winter of 1998-1999.[8] Of these cases, 130 (87.8%) were secondary to Influenza A and 17 to Influenza B. These patients presented with cough, vomiting, altered state of consciousness and convulsions, not unlike the four cases notified in Texas, with the only difference being that mortality in Morishima et al.'s series was 31.8% and disability was 27.7%.

The risk of encephalitis is greater in children under the age of 5 years;[9] the clinical signs may present as soon as the first day of symptoms. The virus invades the nasal epithelium and reaches the brain via the olfactory nerve; the influenza A virus (H3) is more pathogenic and invasive than the influenza B virus.

Transverse myelitis, as well as Guillain-Barré syndrome (GBS), have been reported following flu vaccination.[10] In recent years, attention has been paid to the possible relationship between the flu virus and GBS. This year Sivadon-Tardy et al.[11] published a study in which they reviewed the cases of 405 patients admitted with a diagnosis of GBS at a French reference centre between 1996 and 2004; in 234 of them no causal agent had been identified. Attempts are under way to try to replicate their findings in various parts of the world. The authors correlated the cases with the monthly incidence curves of the flu and concluded that 73 patients presented symptoms of GBS during the months when it would be more likely for them to be related to the flu. Among these, there was serological evidence of Influenza A in 13.7% of the cases and of Influenza B in 5.5%. The flu-related cases appear to have a better prognosis than those related to Campylobacter jejuni; they have a lower risk of requiring mechanical ventilation, they come from upper respiratory infections and the interval between the infectious episode and the onset of GBS is longer. In short, during times of peak incidence of flu, these viruses must be considered as a possible aetiology for GBS.

The flu virus is associated with other neurological problems having a higher risk and worse prognosis: Reye's syndrome and acute necrotizing encephalopathy.

In general, the neuropaediatricians and paediatricians must be prepared for consultation on a variety of neurological and neuropsychiatric manifestations associated with influenza A (H1N1) infection.

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Migralepsy; a controversial entity

Migralepsia, una entidad controvertida

Dear Editor,

The term migralepsy was used for the first time in 1960 to describe a case of ophthalmic migraine followed by typical symptoms of epileptic seizure.[1] But it is not until 2004 that migraine-triggered epilepsy or migralepsy was included (under point 1.5.5) in the 2nd edition of the International Classification of Headache Disorders (ICHDII)[2] where it is defined as an epileptic seizure occurring during or within 1 hour after a migraine aura.

We report here the case of a 15-year-old female with a family history of migraine with aura (father and grandmother). From the age of 10 years, the patient had presented paroxysmal seizures with a visual aura in the form of flashes of light and zigzagging lines in the centre of her field of vision, moving slowly and crossing over each other. After 20 or 30 minutes, she presented clonic movements on the right hand side of her body, occasionally extending into generalized seizures in which she lost consciousness, with tonic-clonic jerking in all four limbs. These seizures continued with intense left hemicranial cephalea accompanied by photophonophobia and nausea. She was initially diagnosed as having migraine with aura and treatment was begun with gabapentin at a dose of 300 mg every 12 h. Subsequently, an electroencephalogram (EEG) was performed while she was awake and this revealed an acute left temporal focus; she was then diagnosed as having complex focal epilepsy and treatment was begun with levetiracetam 2,000 mg/day. At age 15, she was once more admitted to our department following a new episode. Magnetic resonance (MR) scan of the brain presented no alterations. The EEG in vigil revealed persistent acute activity in the left temporal region figure 1. The patient and her family reported 1 to 2 episodes per month despite good compliance with medication. In view of the diagnosis of migraine-induced epilepsy, it was decided to replace her treatment with 600 mg per day of valproic acid; after 8 months of follow-up, total remission of her clinical symptoms has been achieved, with a slight asymmetry in the check-up EEG in vigil.

The theory most commonly accepted with respect to the pathophysiological substrate of migraine aura is the phenomenon of propagated cortical depression. This phenomenon consists in a wave of neuronal and glial depolarization extending from the visual area throughout the occipital pole (visual aura) and, less frequently, to the parietal sensory cortex (sensory aura) and the motor area (motor aura); thus, hypoperfusion/hypometabolism occurs in the area.[3] This cortical depolarization is capable of activating the trigeminal-vascular system, inducing the release of vasoactive peptides (CGRP and VIP) in the leptomeningeal area, giving rise to vasodilatation and sterile inflammation causing migraine pain.[4] Migraine aura and epilepsy share a common pathophysiological substrate. On the one hand, depolarization processes are activated during the propagated depression phenomenon, involving stimulant amino acids and their receptors (glutamate and NMDA receptors) which also participate actively in epileptic seizures. On the other hand, the biochemical mechanism of propagated depression gives rise to a state of local hyperexcitability with certain similarities with the increased stimulant tone involved in the pathophysiology of epilepsy.[5] Therefore, in both entities there is a state of cerebral hyperexcitability that would be more marked in epilepsy than in migraine aura and intermediate in migraine-induced epilepsy.

There is evidence that migraine *per se* may represent an epileptic seizure and may even in some cases be the sole manifestation of epilepsy.[6] For this reason, it is recommended to perform an EEG during and between migraine crises in selected patients with prolonged episodes of migraine or poor response to treatment.[7]

Our patient presented recurrent bouts of focal epileptic crises in the course of her visual migraine auras and fulfilled the current diagnostic criteria of the ICHDII for migraine-induced epilepsy (table 1). There are some discrepancies with respect to these criteria, as set out in the papers by Maggioni et al.,[8] who present several cases of epileptic seizures preceded by migraine without aura and propose to include epileptic seizures triggered by a migraine with or