PRELIMINARY EXPERIENCE OF THE CLINICAL AND TOMOGRAPHIC CHARACTERISTICS OF PATIENTS WITH NON-REFRACTORY ACUTE RESPIRATORY INSUFFICIENCY CAUSED BY H1N1 INFLUENZA A VIRUS INFECTION AND INTERVENTION OF DISEASE.

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Citation

Abstract

Introduction- The H1N1 Influenza A virus infection has a rapid spread worldwide, and although it is believed to have a low mortality rate, once the virus reaches the acute refractory respiratory insufficiency phase, the mortality rate increases drastically.

Materials and Methods- In this study we report the results of 10 clinical case studies of patients who arrived at the emergency room of the Military Hospital located in Guayaquil, Ecuador during the months of July 22, 2009 through September 11, 2009. Upon arrival the patients presented signs and symptoms of acute respiratory insufficiency and were positive for the H1N1 Influenza A virus. The data presented in this paper emphasises the clinical manifestations, arterial blood gas analysis and high resolution computerized tomography (HRCT) findings.

Result: The characteristics of the patients studied were the following: Mean age of 28.5 +/- 15.4 SD. The mean time of patient hospitalization was 12.5 days +/- 10.9 SD. The mean values of Interleukin 6 were: 17.8 +/- 9.9 SD. The mean level of SaO2% was 91.3 +/- 2.5 SD. The mean values for respiratory rate were 28.8 +/- 4.2 SD. The mean level of arterial pH was 7.35 +/- 0.06 SD. The mean values of arterial PCO2 were 40.75 +/- 7.99 SD. The mean values of arterial PO2 were 59.99 +/- 9.36 and the mean values of arterial H3CO were 22.06 +/- 5.28. The most frequent findings on high resolution computerized tomography findings were: thickening of the peribronchovascular space (90%), followed by intralobular septa thickening (50%), subpleural septa thickening (30%), bronchioectasis (40%), mosaic image of perfusion (40%) and pulmonary condensation zones (30%). Two patients required non-invasive mechanical ventilation which was set to low exhaled tidal volume of 200mL for the patient weighing 42kg and 300mL for the patient weighing 60kg. We believe that the findings on the HRCT in these patients represent a precocious interstitial lung lesion; for which we consider that an early intervention could prevent the disease progression and the onset of the refractory phase that subsequently leads to hypoxemia and diffuse alveolar damage

INTRODUCTION

Since April 2009 the World Health Organization (WHO) has reported cases of patients infected with the new H1N1 Influenza A virus in Mexico and The United States, with a rapid worldwide spread. (1). In Ecuador the first reported case of H1N1 Influenza A virus occurred on May 15, 2009; the patient was a child from Guayaquil who had recently traveled to Miami.

On June 11th, 2009 the World Health Organization classified the spread of the disease as an imminent pandemic (stage VI according to the WHO classification). This level of alert does not specify the clinical severity of the disease; instead it classifies the geographical extension. Even though the rate of mortality of the disease has been low so far, the evolution of the virus is unpredictable. (2)

The course of the disease has a wide spectrum of clinical findings, ranging from patients who present with no fever and mild infections of the lower respiratory tract to fatal pneumonias leading to respiratory distress. In this article we present the description of 10 case studies of acute respiratory
insufficiency and infection due to H1N1 Influenza A virus, emphasizing on the clinical manifestations, arterial blood gas analysis and high resolution computerized tomography (HRCT) findings.

The treatment protocol applied for early medical intervention is also proposed in this article, which consists of oseltamivir, antibiotics, bronchodilators, low dose corticosteroids and Non Invasive Mechanical Ventilation (NIMV).

MATERIALS AND METHODS
This research study was performed at Guayaquil’s Military Hospital, in the city of Guayaquil, Ecuador. The Military Hospital is a medical center specialized in the treatment and management of patients presenting with diseases related to the respiratory system. The area designated for respiratory pathologies consists of 24 beds and specialized equipment for the treatment, evaluation, and management of patients with respiratory pathology.

SELECTION CRITERIA
All patients who arrived to the ER at the Military Hospital from July 22, 2009 through September 11, 2009 presenting symptoms suggestive of H1N1 Influenza A virus.

Consent was obtained from the patients or their relatives if they were unable to do so. This study was approved by the Ethics Committees from “University of San Francisco de Quito” and by the Military Hospital in Guayaquil – Ecuador.

Clinical symptoms included: fever >38.5°C, arthralgias, myalgias, headache, nasal obstruction, productive cough, and acute respiratory insufficiency. (Respiratory rate > 25 breath for minute and hypoxemia measured by a partial pressure of arterial oxygen (PaO2) < 60 mmHg.

Non refractory acute respiratory insufficiency and H1N1 Influenza A.- All the patients who at the time of the emergency room evaluation presented with a respiratory rate greater than 25 per minute, with or without bronchospasm and an O₂ Saturation < 93 % without complementary oxygen where placed into the non refractory acute respiratory insufficiency group.

Interventions and Measurements.- After performing a nasopharyngeal swab to all patients who presented with the signs and symptoms suggestive of H1N1 Influenza A, the samples were gathered and then evaluated for quantitative C-reactive Protein levels CRP. CRP, is a marker for bacterial infection and inflammation. CRP was measured by immunoturbidimetry in an automatic autoanalyzer HITACHI 747 using a commercial kit (Roche Diagnostics Systems). The upper normal limits were 5 mg/L \textsuperscript{-1} for CRP.

The sample was also evaluated for a complete blood count, LDH levels, and serum Interleukin 6 levels. Radiologic studies were performed on each patient, and they included a Standardize PA and Lateral chest X-ray followed by HRCT. Additionally blood samples for culture studies, urine culture and a sputum culture were collected for further analysis.

Sampling for H1N1 Influenza A.- Specimens from nasopharyngeal swab were collected and stored at a specific temperature of 2 – 4 °C in order to ensure their adequate transportation to the “Instituto Nacional de Higiene de Guayaquil”, were the microbiology department of the Public Health Ministry MSP performed the sample processing. RT-PCR tests were done according to standardized guidelines provided by the U.S. Center for Disease Control and Prevention.

Radiologic and Tomographic studies.- Standardized PA and Lateral chest X-rays were obtained from every patient. 10 mm sections from computed axial tomography with contrast injection were executed and then followed by a 1.5 – 2 mm section in high resolution computerized tomography findings (HRCT). All scans were carried out at full inspiration. Radiological studies were performed by two experienced radiologists.

EARLY INTERVENTION PROTOCOL
Oxygen therapy. - All patients received supplemental oxygen by means of nasal cannula, avoiding the high oxygen concentration to maintain the partial pressure of arterial oxygen (PaO2) between 100 -105 mmHg.

Bronchodilator therapy. – We used 200mcg (Albuterol)/36mcg (Ipatropium Bromide) every 2-4 hours with a metered-dose inhaler with a space (AeroChamber).

Corticosteroids therapy. - It was initiated early in the treatment course in patients who presented bronchospasm and high systemic inflammatory response reflected by high levels of Interlukin 6. We combined low-dose hidrocoristone (100 mg every 8-12 hours) with inhaled corticosteroids (Budesonide 400 mcg + Formoterol) in patients who presented acute respiratory insufficiency, (with respiratory
rate between 25-40)

Antibioticotherapy. - All the patients with elevated levels of quantitative PCR > 5 mg/L, received ampicilline/sulbactan in a dose of 3g IV every 8 hours in order to treat bacterial infection

Antiviral therapy. - We used to oseltamivir in all our patients in doses of 75 mg, every 12 hours since the initial diagnostic confirmation for the disease.

**NIMV PROTOCOL**

For the NIMV support we used a KnightStar® 335. (manufactured by Puritan-Bennett Corporation Tyco Healthcare UK ) The control settings were placed at A/C modality with BACKUP f (respiration rate of 15) and ISENS 3, ESENS 3, RISE TIME 20. IPAP and EPAP levels were initially set to 11 cm H2O and 6cm H2O, respectively. We use one types of interface devices the Ultra Mirage series III (manufactured by Resmed).

NIMV therapy was initiated on a non-interruption 6 hour mode that was carefully monitored by a Respiratory Technician, an NIMV – Trained Medical Resident, or by the Attending Physician. The initial 6 hour setting was later changed to a 3 hour interval setting, in which the tolerance and patient response were monitored by a Respiratory Technician or the head Nurse. Weaning was initiated after correct stabilization of clinical parameters. We pursued this protocol as long as the patient’s tolerability allowed it. All data were expressed as mean +/- SD for all numeric variables and percentages for all the nominal variables.

Results.- The mean age was 28.5 +/- 15.4 SD, the mean hospitalization time was 12.5 days +/- 10.9 SD, the mean days from the beginning of symptoms until admission was 2.4 +/- 0.7 SD. The mean temperature was of 38.9 °C +/- 0.6 SD. Descriptive variables were as shown in Table 1.

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**Table 1. Descriptive characteristics of the 10 patients with H1N1**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Minimum</th>
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<th>Maximum</th>
<th>Std. Deviation</th>
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<tr>
<td>E B P</td>
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<td>24.0</td>
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<td>HCO3</td>
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<td>22.0</td>
<td>26.0</td>
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</table>

HCT= Hematocrit; MCV= Mean corpuscular volume; MCH= Mean corpuscular hemoglobin; BMI= Body mass index; LDH= Lactate dehydrogenase in peripheral blood; MCC= Concentration mean corpuscular; LDH= Lactato Deshidrogenasa en sangre periferica; Na= Sodium concentration in plasma; K= Potassium concentration in plasma; Cl= Chlorine concentration in plasma; SaO2% by Pulse Oximetry= Peripheral oxygen saturation measured in finger; HR= Number of heart beats in 1 minute; RR= Number of respirations in 1 minute; pH= Hydrogen ions concentration; PCO2= Partial pressure of Carbon Dioxide; EBP= Excess of base; H3CO= Bicarbonate concentration in blood

The most frequent symptoms were fever, cough, and sputum production as shown in table 2
All the radiologic findings are shown in table 3 as well as the computerized tomographic image results. The most frequent findings on HRCT were: thickening of the peribronchovascular space (90%), followed by intralobular septa thickening (50%), subpleural septa thickening (30%), bronchiolectasis (40%), mosaic image of perfusion (40%) and pulmonary condensation zones (30%). (Shown in table 3,4 and pictures 1,2,3,4) From our 10 case studies, only 2 of our patients required NIMV, which is shown in table 5.
Figure 6
Picture 1: Bilateral cylindrical bronchioectasis in lateral basal segments

Figure 7
Picture 2: Thickening of subpleural septa and atelectasic bands

Figure 8
Picture 3: Thickening of peribronchovascular space and subpleural septa

Figure 9
Picture 4: Thickening of intralobular and subpleural septa with condensation zones in lingular left inferior segment

DISCUSSION
The purpose of our study was to describe the clinical manifestations, as well as the laboratory and radiologic findings of 10 patients who tested positive for H1N1 Influenza A with non-refractory acute respiratory insufficiency.

From the results of our study we could observe a marked predominance of the disease for young patients (mean of 28.5 years ± 15.4 SD). The most common symptoms that our patients presented were fever and a productive cough accompanied by arthralgias and myalgias. These findings were consistent with the Mexican group’s study guided by Pérez-Padilla R et al. (1)

For the 10 patients the mean body mass index was 25, with a range of 13.7 – 33.3. It has been observed and reported in other studies that a high body mass index is correlated with a poor disease prognosis and outcomes. (3)

The most common findings in HRCT were: thickening of the peribronchovascular space which was seen most frequently, and thickening of the intralobular and subpleural septa.

These 10 patients presented elevated levels of IL-6 in peripheral blood samples (mean 17.8 ; range: 2 – 33.8) , showing that the damage and clinical course of the illness depend on the immunologic reaction mediated by inflammatory cytokines in response to viral replication. Even though all cultures were negative, the possibility of concomitant bacterial infection should be taken into consideration because elevated levels of quantitative PCR were seen in our patients (mean 35.7). Patients with the
highest PCR levels (mean 59.3; range: 22.3-121.5) also had most altered findings in the HRCT.

It has been observed that PCR can be used as a marker of disease severity in patients with respiratory tract infections. Several studies demonstrate that levels above 50 mg/dl have a greater probability of complications (PCR levels might be a valuable tool that can aid clinicians in properly identifying clinically relevant infections and improve therapeutic decision making). However the PCR measurements do not allow specific predictions for microbial etiologies which can affect the lower respiratory tract.

Only 2 of the 10 patients had a concomitant neuromuscular disorder which according to what we could observe, this baseline disease affected the course of the H1N1 Influenza A virus infection, making the respiratory insufficiency more profound and severe.

We also discovered that those patients who received NIMV had associated neuromuscular alterations during the treatment course.

The majority of complications in patients with H1N1 Influenza A have been reported in patients with concomitant medical conditions; however, the highest mortality rates are seen in young patients without other medical conditions.

We believe that our sequential treatment for non-refractory acute respiratory insufficiency with oxygen, bronchodilators, low doses of corticosteroids, and NIMV, prevented the use of invasive mechanical ventilation.

In this study, we established that the use of NIMV in the early stages of the disease might be of great value. Of the 10 patients, the 2 who had neuromuscular co-morbidity were given NIMV. Although NIMV is not recommended for patients with refractory hypoxemia and shock, we consider that earlier intervention could alter the disease prognosis ultimately producing a more favorable outcome. For those patients with refractory hypoxemia the NIMV was set to low exhaled tidal volume of 200mL for the patient weighing 42kg and 300mL for the patient weighing 60kg. The mechanical properties of the 2 patients that received NIMV suggests that addressing the neuromuscular problem firts could be determinant for the successful recovery of these patients. One 21 year old male patient, without any co-morbidities had a successful recovery with the use of Bilevel mode mechanical respiration (BiPAP: Bilevel positive airway pressure).

We used oseltamivir in all our patients in doses of 75 mg, every 12 hours since diagnosis confirmation. Observational studies now show a significant reduction in mortality rates for patients hospitalized with seasonal influenza compared with those that were not hospitalized. Although early treatment (<48 hours) is ideal, the mortality rate was also reduced when treatment was started >48 hours after diagnosis.

Although the use of corticosteroids is not recommended in patients with H1N1 Influenza A, we combined a low-dose hydrocortisone (100 mg every 12 hours) with inhaled corticosteroids (Budesonide 400 mcg + Formoterol) in patients who presented acute respiratory insufficiency, measured by the respiratory rate of 28.2 (24-40), and bronchospasm. Confalonieri M et al (12) and Annane D et al (13) recommend the use of corticosteroids in patients who present specific conditions associated with pneumonia and to prevent the evolution to septic shock. Whatever the use of low dose corticosteroids in 5 of 10 patients with acute respiratory failure and novel H1N1 Influenza A, has also been reported.

We believe that the findings on the HRCT in these patients represent that the role of the initial interstitial lung lesion is key in formulating an early intervention plan that could prevent disease progression, and the further onset of the respiratory complications like the refractory respiratory insufficiency, hypoxemia and diffuse alveolar damage.

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