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Characteristics of Influenza A/H1N1 complications: ARDS, pneumonia, acute kidney failure, sepsis - review

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Abstract

Type A h1n1 influenza got its start in 2009 during a pandemic that swept across many countries and contributed to massive mortality. It was characterised by its prevalence among young adults and children.

It was associated with fairly common symptoms such as cough, fever and muscle aches, yet it spread rapidly and caused many complications, mainly involving the respiratory system, but also the nervous, circulatory and urinary systems. They often led to long hospital stays and differed in their course and clinical picture from the same diseases of other aetiologies.

The aim of this paper is to present the most common complications and demonstrate these differences.

Keywords

Influenza, complications, influenza a, ARDS, pneumonia, acute kidney failure, sepsis

Introduction

One of the largest pandemics prior to the SARS-COV2 pandemic was the H1N1 influenza A virus. (1) On 11 June 2009, a swine flu pandemic was declared, starting an outbreak of respiratory illness in Mexico. (2) It spread from person to person to over 214 countries and communities in one year. (3) The first similar pandemic occurred as early as 1918. initiating seasonal epidemics of varying severity. (4) This was influenced by the high genomic variability of the virus making it difficult to control its spread and to create usefull vaccine.(4) The virus, belonging to the Orthomyxoviridae family, is characterized by its capacity for genetic reassortment, antigenic drift, and shift, which complicates epidemiological control.(5) Epidemiological studies highlighted the distinct clinical presentations and demographic vulnerabilities associated with H1N1 infections, showing differential impacts across age groups and comorbid conditions.(6)

In severe cases of the 2009 H1N1 pandemic, the clinical presentation differed significantly from that observed during seasonal flu epidemics, with a notable number of those affected being previously healthy young individuals.(7) The high incidence mostly affects children and young adults. (2) Critical illness has been uncommon in patients over 60 years old, and hospitalized individuals often do not have underlying chronic conditions. As of now, there have been 300,000 confirmed cases and 3,917 deaths, resulting in a case fatality rate of 1.3%. (8) Most of the patients were treated with oseltamivir: the recommended schedule was 75 mg twice a day for five days, but the majority of them received higer dose for a longer period. (9,10) While seasonal influenza generally exhibits a consistent pattern of clinical manifestations, the H1N1 strain is linked to a broader spectrum of complications, with many of these diverging significantly from those associated with other influenza virus subtypes.

Complications of Influenza A H1N1

Initial reports of pH1N1 cases in the United States suggested that most patients experienced mild symptoms. Among those with more severe illness, the primary complications were respiratory failure, resembling ARDS, and a prolonged recovery period. (8) Common symptoms include cough, fever, sore throat, muscle pain and headache. Its course is usually mild, although it can take more aggressive forms, leading to severe complications. (2) Complications mostly involve the respiratory system, e.g. pneumonia, severe respiratory distress syndrome, pleural empyema, hemoptysis, pneumothorax. They also affect the circulatory system, e.g. possible myocardial infarction, arrhythymia, hypertension, sepsis or neurological complications. (11) Influenza's indirect effects on underlying heart conditions, such as congestive heart failure and ischemic heart disease, seem to have a greater influence

on cardiac-related health issues. Strong observational evidence highlights the association between influenza infection and a higher risk of acute myocardial infarction and death. (8) Neurological complications include seizures and encephalopathy, which are significantly more common in children. (11) In comparison to seasonal influenza, a slightly smaller amount of patients in the pH1N1 group experienced complications; however, a greater percentage needed either invasive or non-invasive ventilatory assistance. Nelson et al. observed that while pneumonia and acute airway conditions were the predominant complications in both cohorts, extrapulmonary complications (neurologic, gastrointestinal, and renal issues) were notably more prevalent among patients with pH1N1 influenza. Additionally, lymphopenia and increased transaminase levels were more commonly recorded in individuals infected with pH1N1.(12)

Purpose

In this paper, we would like to present the review of literature on differences in the clinical course of its most common complications in relation to the same conditions with other aetiologies.

ARDS

ARDS is a type of respiratory failure characterised by inflammation and pulmonary edema.(13) It presents with bilateral pulmonary parenchymal infiltrates visible on X-rays and a PaO2 /FiO2<200 ratio resulting from causes other than acute left ventricular dysfunction.(14) The causes of the syndrome can be a variety of diseases including infectious pneumonia, absorption of gastric contents, severe trauma, fat embolism, drugs, superficial skin burns, massive blood transfusions and mainly sepsis. (14) In the case of ARDS associated with Infuenza H1N1 virus infection, there is a very severe course, refractory to treatment. (14) Acute respiratory distress syndrome (ARDS) caused by influenza A (H1N1) infection can cause critical hypoxaemia, requiring high ventilator settings, use of unconventional modes and, in some cases, extracorporeal blood oxygenation. (15) Compared to COVID-19-induced ARDS, patients with ARDS from influenza A infection have more pronounced indicators of inflammation and oxidative stress. COVID-19 instead causes a significant deficit in energy supply, which induces additional energy production pathways. Covid-19-induced ARDS relative to IAP results in different regulation of amino acid metabolism, lipid metabolism, glycolysis and anaplerotic metabolism.(13) In a retrospective study by the Department of Anesthesiology and Intensive CareMedicine, Charité-Universitätsmedizin Berlin, it was shown that gas exchange was more severely impaired over

time in patients with H1N1-ARDS compared with ARDS of other origins. ECMO was needed more often in these patients and hospitalisation was significantly prolonged, which did not affect the differences in mortality. (14) Ventilation for more than 7 days is typically considered an exclusion criterion for ECMO treatment, although this criterion can vary across different studies. Some research suggests that younger patients may tolerate longer ventilation times, even beyond 9 days, and still benefit from ECMO treatment. It is well established that both the duration of high pressure/high FiO2 ventilation and the patient's age are key factors contributing to ventilator-induced lung injury. Since patients with influenza A (H1N1)-related ARDS tend to be younger, they may be more capable of withstanding extended ventilation periods without a higher risk of mortality. (16) ARDS caused by H1N1 influenza can cause very severe hypoxaemia. This is likely to be due to a virulent viral infection inducing an abnormal immune response that leads to extensive lung damage. This is indicated by increased numbers of CD8+ T lymphocytes and granzymes in the lung tissue. (15) A 2012 prospective observational study found that one year after ICU discharge, survivors of ARDS caused by A(H1N1)-related pneumonia experienced only mild disabilities. Most had no noticeable weakness based on MRC testing, had returned to work, and some were regularly engaging in sports. While pulmonary function was nearly normal, many patients showed reduced diffusion capacity across the blood-gas barrier and had limitations in physical exertion.(17)

Pneumonia

Pneumonia is a serious infectious disease that often leads to prolonged hospitalisation and even death. (14) Many microorganisms can cause pneumonia, but the growing importance of viruses as a cause of pneumonia in children is now receiving increasing attention. The emergence of Severe Acute Respiratory Syndrome (SARS), Avian Influenza A (H5N1) and Pandemic Influenza A (H1N1) virus in 2009 has again highlighted the role of viruses as a cause of severe pneumonia. (15) During pandemic (H1N1) 2009, the incidence of pneumonia in hospitalised patients ranged from 23% to 66%, which was the most common complication.(18) It is the most common complication of influenza A(H1N1) and occurs most often as primary viral pneumonia or secondary bacterial pneumonia. Patients with secondary bacterial pneumonia compared to primary viral pneumonia were proven to have more frequent chronic liver disease, purulent sputum, tachycardia, exudative pleuritis and CRP above 80 mg/L. In contrast, bilateral interstitial chest infiltrates on X-rays were more common in viral. (2) In comparison to pneumonia of other origin than influenza A(h1n1) virus, these patients were younger. Furthermore, the analysis by Chang et.al showed that the presence of

conditions predisposing to influenza complications were common in both groups, but more so in patients with inflammation of other origin than influenza A(H1N1) virus.(14) Studies have indicated that patients infected with influenza A (H1N1)pdm09 often present with both hypocalcemia and hypochloremia. While hypocalcemia can be associated with alkalosis, this association was not observed in these patients, as their blood pH did not differ significantly from that of patients with non-(H1N1)pdm09 pneumonia. This suggests that the mechanisms underlying electrolyte imbalances in influenza A (H1N1)pdm09 infections may differ from those typically seen in conditions associated with respiratory alkalosis. Influenza A (H1N1)pdm09 has been associated with rhabdomyolysis, which can lead to hypocalcemia due to the release of intracellular calcium from damaged muscle tissue. This suggests that electrolyte imbalances in these patients may result from multiple factors. Awareness of this complication is important in managing severe influenza cases. Hypochloremia on the other hand is often associated with acidosis and can be a consequence of hypoventilation; however, in patients infected with influenza A (H1N1)pdm09, the expected pattern of hypoventilation was not observed. When compared to patients with non-H1N1pdm09 pneumonia, those with influenza A (H1N1)pdm09 did not demonstrate signs of hypoventilation. This suggests that the alterations in chloride levels in these patients may occur through mechanisms other than respiratory failure or hypoventilation, indicating a potentially unique pathophysiological response to the infection.

Further investigation into the underlying causes of these electrolyte imbalances in the context of H1N1 pneumonia may be warranted.(19)

A frequent association with obesity in patients with 2009 A(H1N1) influenza infection was also indicated. Furthermore, more non-specific symptoms have been noted in these patients, such as headache , myalgia and fatigue.(14)In H1N1 infection especially with pneumonia, the use of antiviral drugs even 48h after the onset of infection is recommended to reduce complications. (15) Evidence derived from health care claims indicates that the clinical advantages of oseltamivir may go beyond alleviating the severity and duration of influenza symptoms to also lowering the risk of pneumonia.(10) Treatment with Oseltamivir lowers the incidence of lower respiratory tract complications, decreases antibiotic prescriptions, and reduces hospitalization rates in both healthy adults and those considered at-risk. (9) Studies have shown that the initial CRP in these patients was significantly lower than in inflammations of other origins. (14) Moreover mortality was twice as high in pandemic patients as in those infected with seasonal influenza(12% to 5%).This difference was nevertheless not statistically significant(p=0.238) (20) The characteristic lesion on chest X-

ray as well as on CT is the bilateral matted glass image and consolidations seen in the vesicles. On X-ray, these lesions are seen at the base of the lungs and in the central part, whereas on CT they are peripheral and peribronchiolar with areaic spillage. CT relative to X-ray is more effective in diagnosing uncertain cases.(30)(21)(22) Several studies have evaluated the use of corticosteroids as an adjunctive treatment for in-hospital patients with community-acquired pneumonia. However, many of these had quite a few deficiencies and did not directly address ah1n1 influenza pneumonia. The study by Emili Diaz et al. on the other hand, was limited to patients with primary viral pneumonia and did not find potential benefits from their use.(23)

Acute renal failure

During the 2009 pandemic, the majority of A/H1N1 virus complications were respiratory, but we must not forget the severe complication of acute kidney failure. In cases diagnosed in Mexico, the incidence of AKI oscillated around 30%. Similarly, in the Austin hospital, out of 13 cases, eight developed AKI. Among patients with AKI, in-hospital mortality was around 25% (24) and renal replacement therapy was needed in 1 in 3 cases. AKI associated with H1N1 2009 influenza is also associated with higher CK levels. Based on histopathological findings of myoglobin deposits in tubules in some patients, AKI is due to rhabdomyolysis. (25)

H1N1-induced AKI has a multifactorial origin-acute renal tubular necrosis due to hypoxaemia resulting from acute lung injury, hypoperfusion, renal vasoconstriction and rhabdomyolysis in the setting of a severe systemic inflammatory response syndrome with a cytokine cascade. (26) Patients with A/H1N1 virus and ARDS who developed AKI showed higher levels of circulating C-peptide, insulin, procalcitonin, serum amyloid A and leptin than patients without AKI. After adjusting for confounding variables, we found that elevated circulating C-peptide levels and BMI > 30 kg/m2 were significantly associated with a higher risk of developing AKI in patients with ARDS. (27) Most patients who faced renal failure requiring dialysis recovered, with 10 out of 11 patients (89%) returning to health. This outcome is not unexpected considering their youth and various comorbidities. Numerous large observational studies have indicated a heightened risk of chronic renal failure, end-stage renal disease, and mortality among individuals who experience acute kidney injury (AKI) that necessitates temporary dialysis.(28) A case series from the Austin Hospital, along with findings from other institutions, largely agree that a considerable percentage of adults with 2009 H1N1 who were admitted to the ICU experienced acute kidney injury (AKI) and faced a high rate of mortality during their hospital stay. Renal replacement therapy (RRT) was deemed necessary for about

one-third of these patients.(29) The study by Regina et al. highlighted that AKI was one of the more severe complications of H1N1-related illness. This was evidenced by higher APACHE II scores and greater functional impairments, including pulmonary and hepatic dysfunction, observed in patients with AKI. Additionally, the combination of H1N1 infection and AKI was strongly linked to hemodynamic instability during ICU stays, with 79% of these patients requiring vasopressor support.(30)

Sepsis

Sepsis is defined as a potentially life-threatening condition that involves organ dysfunction resulting from an inappropriate immune response to an infection. The primary causes of sepsis include infections from bacteria, fungi, and viruses.

The dysregulated host response seen in sepsis is intricate, involving both factors related to the pathogens and inflammatory responses mediated by immune cells. These immune reactions can lead to detrimental effects, particularly in the early or advanced stages of the condition.(31) While all influenza viruses are capable of infecting the respiratory epithelium, ranging from the upper airways to the alveoli, different strains exhibit varying patterns of infection. Seasonal H3N2, H1N1, and typical influenza A viruses primarily cause inflammation and epithelial necrosis in the large airways, including the trachea, bronchi, and bronchioles. In contrast, more virulent strains such as the 1918 H1N1, the pandemic 2009 H1N1, H5N1, and certain influenza A viruses tend to affect not only the large airways but also involve the alveoli more frequently, leading to more severe respiratory complications.(32)Viral infections like the influenza virus can also disrupt the innate immune system, resulting in an overproduction of cytokines and potentially harmful effects. An abnormal immune response to influenza can cause damage to the endothelium through changes in the cellular cytoskeleton, loss of intercellular junction integrity, and cell death. This dysregulation can affect coagulation processes, leading to changes in microvascular permeability, tissue swelling, and shock. (32) Influenza A (H1N1) is associated with a "cytokine storm," a pathogenic mechanism where the virus triggers an excessive immune response. The study from Eric et al. supports the notion that blood cytokine levels were generally higher in patients with influenza A (H1N1)pdm09 compared to those with non-(H1N1)pdm09 pneumonia, particularly for IL-8, IL-10, and IL-17.(33)

Conclusion

Complications of the A/H1N1 influenza virus pose a high risk to patients infected with it. They often require admission to an intensive care unit or ECMO. They are also often

associated with atypical symptoms not found in the same conditions of other aetiologies. They are also characterised by different imaging and histo-pathological findings. In addition, they often have a much more severe course and a higher risk of fatal outcome.

Disclosure

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