Study of the outcome of Avian and Swine Flu confirmed cases Admitted in Abbasia Chest Hospital between 2006-2010

Thesis
Submitted for partial fulfillment of the Master Degree
In Chest Diseases

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2011

INTRODUCTION

Influenza is a serious respiratory illness which can be debilitating and cause complications that lead to hospitalization and death, especially in the elderly. Every year, the global burden of influenza epidemics is believed to be 3-5 million cases of severe illness and 300,000-500,000 deaths. The risk of serious illness and death is highest among persons aged > 65 years, children aged < 2 years, and persons who have medical conditions that place them at increased risk of developing complications from influenza.[1]

Influenza type A viruses have conserved their actuality and importance during history with their special respect of genetic variations and global pandemics. In recent years their significance has increased because of the appearance of "bird flu" caused by a highly virulent strain H5N1 subtype. Although influenza type A viruses that cause infections in the birds (avian influenza) are species-specific, some may cross the species barrier to infect humans. Previously, it was thought that direct transmission of virus from bird to human could not take place, but it came to be true in 1997, in Hong Kong. Since avian influenza virus A (H5N1) produces

human infections with high morbidity and mortality rates, the probability of human-to-human transmission and its consequences attract a great deal of attention. [2]

In March, 2009, a novel strain of swine-origin influenza-A H1N1 caused human infection in Mexico, and spread to all regions in the world in the following three months. On June 11, 2009, the World Health Organization declared that a global pandemic of influenza A H1N1 was underway. This action was a reflection of the spread of the new H1N1 virus, not the severity of illness caused by the virus. As of October, 2009, there are about 400,000 confirmed cases and 5000 mortalities due to pandemic H1N1 all over the world. The most important duty against pandemic H1N1 is prevention, which means first of all the adherence of hygienic rules and the use of vaccination.[3]

Aim of the work

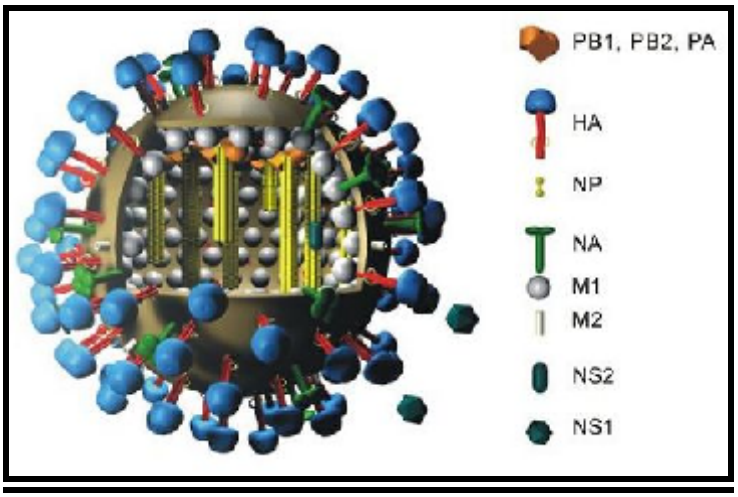
The aim of this study was to evaluate the clinical, epidemiological features and treatment outcome of avian flu and swine flu confirmed cases admitted in Abbasia chest hospital between 2006-2010.

Influenza virus A

Morphology

Influenza A viruses are members of the Orthomyxoviridae family. They are differentiated from type B and C influenza viruses on the basis of the identity of the major internal protein antigens, the nucleoprotein (NP) and matrix (Ml) proteins. On initial isolation, influenza A viruses is small (80 to 120 nm in diameter), pleomorphic particles that later become generally spherical. [4]

Figure 1. ***Structure of influenza A virus*** [5]



These particles consist of a host-derived lipid bilayer envelope in which the virus-encoded glycoprotein HA and neuraminidase (NA) and M2 are embedded; an inner shell of matrix protein; and, at the center, the nucleocapsids of the viral genome. The genome of influenza A viruses consists of eight unique segments of single-stranded RNA, which are of negative polarity (i.e., complementary to the mRNA sense). [6]

The RNA is loosely encapsulated by multiple NP molecules. Complexes containing the three viral polymerase proteins (PB1, PB2, and PA) are situated at the ends of the nucleocapsids. [7]

To be infectious, a single virus particle must contain each of the eight unique RNA segments. Available evidence suggests that incorporation of RNAs into virions is at least partly random. The random incorporation of RNA segments allows the generation of progeny viruses containing novel combinations of genes (i.e., genetic reassortment) when cells are doubly infected with two different parent viruses. [7]

The eight influenza A viral RNA segments encode 10 recognized gene products. These are PB1, PB2, and PA polymerases, HA, NP, NA, Ml and M2 proteins, and NS1 and NS2 proteins. [6]

PB1 polymerase: PB1 polymerase is encoded by RNA segment 2; it functions in the RNA polymerase complex as the protein responsible for elongation of the primed nascent viral mRNA and also as elongation protein for template RNA and v R NA synthesis. PB1 proteins localize in the nucleus of infected cells. [8]

PB2 polymerase: PB2 polymerase is encoded by RNA segment 1; It is a member of the protein complex providing viral RNA-dependent RNA polymerase activity. [8]

PA polymerase: PA polymerase is encoded by RNA segment 3. It also localizes in the infected cell nucleus and is a member of the RNA-dependent RNA polymerase complex along with PB1 and PB2, but its role in viral RNA synthesis is unknown. [8]

Hemagglutinin: The HA protein is an integral membrane protein and the major surface antigen of the influenza virus virion. It is responsible for binding of virions to host cell receptors and for fusion between the virion envelope and the host cell. HA is encoded by RNA segment 4, the HA molecule is highly mutable. In nature, there are presently 14 recognized subtypes of HA , which differ by at least 30% in the amino acid sequence and which are serologically not cross-reactive. [9]

Nucleoprotein: NP is encoded by RNA segment 5. It is transported into the infected cell nucleus, where it binds to and encapsulates viral RNA. In addition to its structural role, NP is believed to play a role in the switching of viral RNA polymerase activity from mRNA synthesis to cRNA and vRNA synthesis. NP is abundantly synthesized in infected cells and is the second most abundant protein in the influenza virus virion. NP is also a major target of the host cytotoxic T-cell immune response. [10]

Neuraminidase: NA, encoded by RNA segment 6, is also an integral membrane glycoprotein and a second major surface antigen of the virion. It functions to free virus particles from host cell receptors, to permit progeny virions to escape from the cell in which they arose, and so facilitate virus spread. Like HA, NA is highly mutable with variant selection partly in response to host immune pressure. Nine subtypes of NA have been identified in nature. [11]

Ml protein: Influenza virus RNA segment 7 is bicistronic, encoding both Ml and M2 proteins. Collinear transcription of segment 7 yields mRNA for the matrix protein. This is the most abundant protein in the influenza virus virion. Matrix protein forms a shell surrounding the virion nucleocapsids, underneath the virion envelope. In the infected cell, it is present in both cytoplasm and nucleus. It has no known enzymatic activity, although it has been speculated to play an important role in initiating progeny virus assembly.[12]

M2 protein: The mRNA for M2 is also transcribed from RNA segment 7. It is derived from the collinear (Ml) transcript by splicing. M2 is an integral membrane protein, whose membrane-spanning domain also serves as a signal for transport to the cell surface. It is present as a tetramer in large amounts on the infected cell surface, and a small amount is found in the virion. It is believed to act as a proton channel to control the pH of the Golgi during HA synthesis and to allow acidification of the interior of the virion during virus uncoating. [12]

Nonstructural NS1 and NS2 proteins: RNA segment 8 encodes the two nonstructural proteins NS1 and NS2. NS1 mRNA is collinear with the vRNA, whereas NS2 mRNA is derived by splicing. These proteins, particularly NS1, are abundant in the infected cell (NS1 primarily in the nucleus, NS2 primarily in the cytoplasm) but are not incorporated into progeny virions. Both proteins play roles in virus replication, but those roles have not been fully defined. NS2 appears to modulate the synthesis of NS. [11]

Serotypes of influenza A virus

Wild aquatic birds are the natural hosts for a large variety of influenza A. Occasionally; viruses are transmitted to other species and may then cause devastating outbreaks in domestic poultry or give rise to human influenza pandemics.[13]

The type A viruses are the most virulent human pathogens among the three influenza types and cause the most severe disease. The influenza A virus can be subdivided into different serotypes based on the antibody response to these viruses. [14]

The serotypes that have been confirmed in humans, ordered by the number of known human pandemic deaths, are:[15]

-H1N1, which caused Spanish Flu in 1918, and Swine Flu in 2009

-H2N2, which caused Asian Flu in 1957

-H3N2, which caused Hong Kong Flu in 1968

-H5N1, which caused Bird Flu in 2004

-H7N7, which has unusual zoonotic potential

-H1N2, endemic in humans, pigs and birds

Hemagglutinin (HA) and neuraminidase (NA) are the two large glycoproteins on the outside of the viral particles. HA is a lectin that mediates binding of the virus to target cells and entry of the viral genome into the target cell, while NA is involved in the release of progeny virus from infected cells, by cleaving sugars that bind the mature viral particles. [16]

Thus, these proteins are targets for antiviral drugs. [17] Furthermore, they are antigens to which antibodies can be raised. Influenza A viruses are classified into subtypes based on antibody responses to HA and NA. These different types of HA and NA form the basis of the H and N distinctions in, for example, H5N1. [18]

There are 16 H and 9 N subtypes known, but only H 1, 2 and 3, and N 1 and 2 are commonly found in humans. [19]

Replication

Viruses can only replicate in living cells. [20] Influenza infection and replication is a multi-step process: firstly the virus has to bind to and enter the cell, then deliver its genome to a site where it can produce new copies of viral proteins and RNA, assemble these components into new viral particles and finally exit the host cell. [21]

Influenza viruses bind through hemagglutinin onto sialic acid sugars on the surfaces of epithelial cells; typically in the nose, throat and lungs of mammals and intestines of birds (Stage 1). [22]

After the hemagglutinin is cleaved by a protease, the cell imports the virus by endocytosis. [23]

Once inside the cell, the acidic conditions in the endosome cause two events to happen: first part of the hemagglutinin protein fuses the viral envelope with the vacuole's membrane, then the M2 ion channel allows protons to move through the viral envelope and acidify the core of the virus, which causes the core to dissemble and release the viral RNA and core proteins. [21]

The viral RNA (vRNA) molecules, accessory proteins and RNA- dependent RNA polymerase are then released into the cytoplasm (Stage2). [24]

The M2 ion channel is blocked by amantadine drugs, preventing infection. [25]

These core proteins and vRNA form a complex that is transported into the cell nucleus, where the RNA-dependent RNA polymerase begins transcribing complementary positive-sense vRNA (Steps 3a and b). [26]

The vRNA is either exported into the cytoplasm and translated (step 4), or remains in the nucleus. Newly synthesised viral proteins are either secreted through the Golgi apparatus onto the cell surface (in the case of neuraminidase and hemagglutinin (step 5b) or transported back into the nucleus to bind vRNA and form new viral genome particles (step 5a). [27]

Other viral proteins have multiple actions in the host cell, including degrading cellular mRNA and using the released nucleotides for vRNA synthesis and also inhibiting translation of host-cell mRNAs. [27]

Negative-sense vRNAs that form the genomes of future viruses, RNA-dependent RNA polymerase, and other viral proteins are assembled into a virion. Hemagglutinin and neuraminidase molecules cluster into a bulge in the cell membrane. The vRNA and viral core proteins leave the nucleus and enter this membrane protrusion (step 6).

The mature virus buds off from the cell in a sphere of host phospholipids membrane, acquiring hemagglutinin and neuraminidase with this membrane coat (step 7). [28]

As before, the viruses adhere to the cell through hemagglutinin; the mature viruses detach once their neuraminidase has cleaved sialic acid residues from the host cell. [28]

Drugs that inhibit neuraminidase, such as oseltamivir, therefore prevent the release of new infectious viruses and halt viral replication. [17]

After the release of new influenza viruses, the host cell dies. Because of the absence of RNA proofreading enzymes, the RNA-dependent RNA polymerase that copies the viral genome makes an error roughly every 10 thousand nucleotides, which is the approximate length of the influenza vRNA. Hence, the majority of newly manufactured influenza viruses are mutants; this causes "antigenic drift", which is a slow change in the antigens on the viral surface over time. [29]