AVIAN INFLUENZA (A) VIRUSES AS A HUMAN PANDEMIC THREAT

Essay

Submitted for Partial Fulfillment of
Master Degree in Clinical Pathology

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2005

ACKNOWLEDGEMENT

First of all, thanks to ***GOD*** whose magnificent help was the main factor in completing this work.

It is a great honor to me to express my sincere gratitude to ***PROF. DR. MAGDA SALAH EL-DIN GABR*** ; Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University for her supervision and helpful discussions and suggestions. In fact, a few words never suffice to do justice in thanking ***PROF. DR. MAGDA SALAH EL-DIN GABR*** for her extraordinary contribution of time, effort and valuable experience.

I wish to express my unlimited gratitude to ***DR. SAMIA ABDOU GIRGIS***, Lecturer of Clinical Pathology, Faculty of Medicine, Ain Shams University. She has unexhausted patience, and she spared no effort at all in following-up this work by precious advice. I can hardly imagine how would this work be completed without her limitless efforts, remarkable suggestions and valuable advice.

Finally, thanks to ***MY FAMILY***, and also thanks to ***ALL THE STAFF MEMBERS OF THE DEPARTMENT*** of Clinical Pathology, Ain Shams University, for their help.

List of abbreviations

NE: Nucleoprotein.
M: Matrix protein.
HA: Haemagglutinin.
NA: Neuraminidase.
NS: Non structural.
NP: Nucleoprotein.
RNP: Ribonucleoprotien.
PA: Polymerase A.
PB1: Polymerase protein B1.
PB2: Polymerase protein B2.
mRNA: Messenger ribonucleic acid.
HPAI: Highly pathogenic avian influenza.
LPAI: Low pathogenic avian influenza.
ATP: Adenosine triphosphate.
WHO: World Health Organization.
IL6: Interleukin 6.
TNF: Tumor necrosis factor.
GTP: Guanosine triphosphate.
HIV: Human immunodeficiency virus.
HLH: Haemophagocytic lymphohistiocytosis.
S.aureus: Staphylococcus aureus.
CD: Cluster of differentiation.
MDCK: Madin Darby-canine kidney cells.
EIA: Enzyme immunoassay.
PCR: Polymerase chain reaction.
HI: Haemagglutination inhibition.
RT-PCR: Reverse transcriptase polymerase chain reaction.
cDNA: Complementary deoxynucleic acid.
RRT-PCR: Real time reverse transcriptase polymerase chain reaction.
Fg: Femtogram
VI: Virus isolation.
CF: Complement fixation.

NT: Neutralization test.
NP: Nasopharyngeal swab.
BAL: Broncho-alveolar lavage.
RSV: Respiratory syncytial virus.
siRNAs: Short interfering ribonucleic acids.
IAV: Influenza A virus.
shRNAs: Small hairpin ribonucleic acids.
dsRNAs: Double stranded ribonucleic acids.
DICER: Double stranded RNA-specific endonuclease.
RISC: Ribonucleic acid interference silencing ribonucleoprotien complex.
PKR: Interferon inducible protein kinase.
WV: Whole virus.
SV: Subviron.
GBS: Guillain Barre syndrome.
IFN: Interferon.
MMWR: Morbidity mortality weekly report.
FDA: Food and drug administration.
CDC: Centers for disease control and prevention.
WER: Weekly epidemiological record.
RNA: Ribonucleic acid.
RT-PCR: Reverse transcriptase-polymerase chain reaction.

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INTRODUCTION

Influenza viruses, which belong to the Orthomyxoviridae family, are classified as A, B and C, based on antigenic differences in their nucleoprotein and matrix protein. All avian influenza viruses are classified as type A. Influenza pandemics which are defined as global outbreaks of the disease due to viruses with new antigenic subtypes which have exacted a high death toll from human populations ***(Horimoto and Kawaoka, 2001).*** They have been responsible for four pandemics of severe human respiratory disease this century ***(Balgent and Mc Cauley, 2003 and Brooks et al., 2004).***

The most devastating pandemic, the so called Spanish influenza of 1918-1919, resulted from an H1N1 virus and caused deaths of at least 20 million people worldwide. Other less catastrophic pandemic occurred in 1957 (Asian influenza H2N2 virus) and 1977 (Russian influenza H1N1) ***(Potter, 1998).*** It is noteworthy that Asian and Hong Kong outbreaks were caused by hybrid viruses or reassortant that harbored a combination of avian and human viral genes ***(Horimoto and Kawaoka, 2001 and Lee et al., 2004).***

In May 1997, an H5N1 virus was isolated from a 3-years old boy in Hong Kong, who died of extensive influenza pneumonia ***(Yuen et al., 1998).*** By the end of 1997, a total of 18 cases of human influenza had been identified, all caused by the same H5N1 virus ***(To et al., 2001 and Kaye and Pringle, 2005).*** Influenza viruses of the H5 type had never been isolated from humans and it is not a reassortant like 1957 and 1968 pandemic strains, instead all viral genes had originated from an avian virus ***(Lu et al., 2003 and CDC, 2004a).***

Although highly pathogenic avian influenza viruses had been identified before 1997 outbreak in Hong Kong outbreak, their devastating effects had been confined to poultry. With the Hong Kong outbreak, it became clear that the virulence potential of these viruses extended to humans by contributing genes to potential new pandemic human strains ***(Balgent and McCauley, 2003 and Hammel and Chiang, 2005).***

AIM OF THE WORK

The aim of this work is to study the epidemiology, interspecies transmission, pathogenicity, prevention and control of influenza A virus, with special emphasis on avian influenza A viruses.

INFLUENZA VIRUSES

Historical Aspects

Influenza virus was one of the viruses that have played a central role in the development of virology. Its name refers to the ancient belief that the disease was caused by supernatural influence. In Florence, during the time of the Renaissance, astrologers linked a curious juxtaposition of stars with an outbreak of influenza infection in the city and attributed it to the "influence" of the stars, hence the name "influenza". Influenza caused major outbreaks of acute respiratory infections many times, so it has been described as (The last great uncontrolled plague of mankind). The isolation of influenza virus from ferret in 1933 was a milestone in the development of virology as a laboratory science ***(White and Fenner, 1994 and Collier et al., 2000).***

Classification

Influenza viruses belong to the Orthomyxoviridae family, this family is divided into four genera, influenza virus A, B, C and thogotovirus ***(Kaye and Pringle, 2005)***, based on antigenic differences in two of the major structural proteins of the virus, the nucleoprotein (NE) and matrix protein (M). All avian influenza viruses are classified as type A ***(Choi et al., 2004).*** Influenza A viruses are further classified into subtypes according to the properties of their major membrane glycoproteins, the haemagglutinin (HA) and the neuraminidase (NA). Sixteen HA subtypes ***(Fouchier et al., 2004),*** and nine NA subtypes now have been identified among influenza A viruses, with minimal serological cross reactivity between

subtypes ***(WHO, 2004b)***. The amino acid sequences of HA1 region, which is responsible for HA antigenicity, differ from subtype to subtype by 30% or more ***(Cox and Zeigler, 2003)***.

Those viruses which have circulated widely in humans «pandemics», are restricted to three HA and two NA subtypes (i.e., H1, H2 and H3 and N1 and N2 subtypes). Most of human influenza A are classified as H1N1 ***(Horimoto and Kawaoka, 2001 and Krauss et al., 2003)***, H2N2 which circulated from 1957 to 1958, however, H1N2 reassortant viruses have circulated in China. The limited array of HA and NA subtypes that infect mammalian host suggest that still obscure genetic and biological factors determine the subtype specificity of influenza A viruses in nature ***(Peiris et al., 2001).***

Nomenclature

The nomenclature of influenza viruses includes the type, the geographic location where the virus was isolated, laboratory identification number, and the year of isolation followed by the subtype for influenza A viruses (in viruses of human origin) e.g., A/ Sydney /7/97(H3N2). The species are included for viruses of non-human origin, e.g., A/seal/Massachusetts/133/82(H4N5) ***(Cox and Ziegler, 2003 and Brooks et al., 2004a).***

Structure and Composition

Influenza A virions are 100-200 nm in diameter and are more or less spherical. The virus is covered with a lipid envelope which is derived from the cell surrounding the virus particle ***(Trampuz et al., 2004)***. The lipid envelope is covered

with about 500 projecting spikes, 10 nm long on the surface of the particle, which can be seen easily under the electron microscope *(Figure 1)* ***(Cox and Kawaoka, 1998; Collier et al., 2000 and Cox and Zeigler, 2003).***

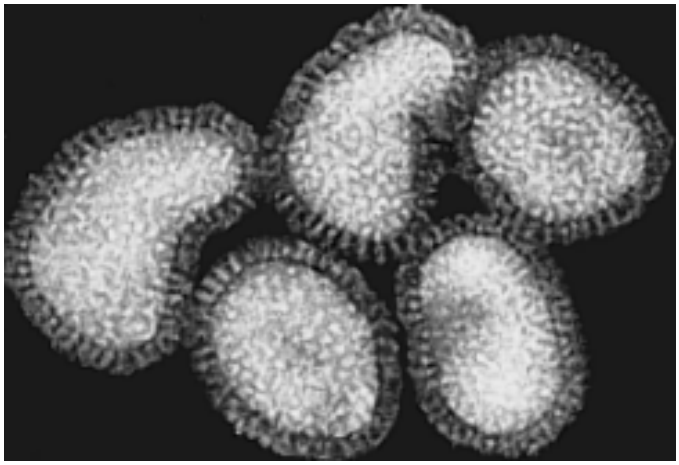

Figure 1: Electron micrograph of influenza virus particles (Ruigrok et al., 1989).

Influenza virus particles *(Figure 2)* contain nine different structural proteins and only one non-structural protein (NS1). The structural proteins include in addition to the HA and NA proteins, the nucleoprotein (NP) which associates with the viral RNA to form a ribonucleoprotien (RNP) structure. The RNP is 9 nm in diameter, assumes helical configuration and forms the viral nucleocapsid ***(Voyles, 2002)***. There is indirect evidence that NP plays a role in host range restriction. For example, replacement of NP gene of avian virus with a NP gene of a human virus alters host range ***(Baum and Paulson, 1991).***

Three large polymerase proteins, designated (PA, PB1, PB2) according to their overall acidic or basic amino acid composition, are bound to viral RNP and are responsible for

RNP transcription and replication**.** The matrix (M1) protein, which forms a shell underneath the viral lipid envelope, is important in particle morphogenesis and is a major component of the virions (about 40% of viral protein). Recent cryoelectron microscopic studies suggest that M1 protein can modify the viral envelope ***(Gomez-Puertas et al., 2000).***

The M2 proteins are thought to function as pH activated ion channel that permit protons to enter the virion during uncoating. The NS2 protein are also present in the envelope but at only a few copies per particle, it is composed of 121 amino acids. It is locating in the nucleus and cytoplasm of infected cells, and is found in virions associated with RNP by interacting with the C terminal portion of M1 protein ***(Horimoto et al., 2004).*** The function of this protein is unknown. The NS2 proteins of type A viruses are more conserved than NS1 protein (76.9% vs. 64.3%); however neither product is conserved to the extent of the other internal proteins ***(Pinto et al., 1992; Cox and Kawaoka, 1998 and Kaye and Pringle, 2005).***

Any protein which is virus encoded but not present in the structure of the virion is considered non structural. The NS1 protein is the only non-structural protein of influenza A virus, NS1 is made in abundance during early infection. It is encoded by mRNA consists of 124-237 amino acids depending on the virus strain and is phosphorylated. It inhibits host mRNA splicing and the nuclear export of the cellular and viral mRNA, maximizing the availability of substrate for capped primers, and thereby promoting viral mRNA synthesis ***(Wagner and Hewlett, 2004).***

The single stranded negative sense RNA genomes of influenza A and B viruses occur at eight separate segments,

influenza C viruses contain seven segments of RNA, lacking a neuraminidase gene ***(Capua et al., 2003)***. Sizes and protein coding assignments are known for all the segments. Most of the segments code for a single protein. The complete nucleotide sequence is known for many influenza viruses. The first 12-13 nucleotides at each end of each genomic segment are conserved among all eight RNA segments, these sequences are important in viral transcription ***(Lund et al., 2004).***

Because of the segmented nature of the genome, when a cell is co-infected by two different viruses of a given type, mixtures of parental gene segments may be assembled into progeny virions. This phenomenon, called genetic reassortment, may result in sudden changes in viral surface antigens, a property that explains the epidemiologic features of influenza viruses and posses significant problem for vaccine development ***(Trampuz et al., 2004).***

Influenza viruses are relatively hardy in vitro and may be stored at 0-4^{o}C for weeks without loss of viability. Lipid solvents, protein denaturants, formaldehyde, and irradiation destroy infectivity. Both infectivity and haemagglutination are more resistant for inactivation at alkaline pH than at acid pH ***(Brooks et al., 2004a).***