DAVETLİ DERLEME (Invited Review)

Determinants Contributing to the Newly Emergent Viruses

Güncelleşen yeni virüslerin ortaya çıkmasını etkileyen faktörler

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Abstract
New viral diseases seem to be emerging globally with increasing frequency. Most of the emerging viruses are zoonotic, that is, communicated by animals to humans. Many different factors can contribute to the emergence of a new viral disease. These factors are: virological determinants, several genetic mechanisms that drive virus evolution such as mutation, recombination and reassortment; individual host determinants such as the host immune response, specific risk behaviors and physiological factors; host population determinants such as human demographics and behavior, international travel and community; environmental determinants such as ecological and zoonotic influences. These determinants need to be understood for prevention and control of emerging viral diseases. Developments in molecular and genetic epidemiology are helping us understand pathogen virulence, transmission patterns, and host susceptibility. Almost always there is a need for epidemiological field investigation to assess the risk to the human and/or animal populations.

Özet
Yeni virüslerin daha çabuk tanımlanmasına bağlı olarak yeni viral hastalıkların ortaya çıkışının hızla artığı görülmektedir. Yeni ortaya çıkan virüslerin çoğu zoonotiktir ve hayvanlardan insanlara bulaşmaktadır. Yeni viral hastalıkların ortaya çıkışında pek çok farklı faktörler katkı sağlar. Bu faktörler: mutasyon, rekombinasyon ve genlerin yeniden yapılanması gibi değişik genetik mekanizmaları içeren virolojik faktörler; konağın immünitesi, davranışı ve fizyolojik durumu gibi bireysel konak faktörleri; insan populasyonunun gelenekleri, uluslararası seyahatleri ve yakın temas gibi konak populasyon faktörleri, ekolojik ve zoonotik çevre faktörleridir. Güncel yeni viral hastalıklardan korunma ve hastalığın kontrolü için bu determinantların iyi bilinmesi gerekir. Moleküler epidemiyoloji alanındaki gelişmeler; virüs virülansının, bulaş şeklinin ve virüse karşı konak duyarlılığının anlaşılmasında yardımcı olmaktadır. Bu nedenle, insan ve/veya hayvan populasyonunun infeksiyon riskini azaltmak için moleküler epidemiyolojik alanda araştırmalara daima ihtiyaç vardır ve yapılmalıdır.

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A newly emerging virus is a virus that has never been recognized before. Previously unrecognized viruses are constantly being identified. New viral infectious diseases emerge as viruses adapt to new hosts and new environments. There is no way to predict when or where the next important new virus will emerge. The newly emerging viral diseases like Severe Acute Respiratory Syndrome (SARS), Nipah virus encephalitis, Lassa fever, swine flu, and human disease caused by the H5N1 strain of avian influenza virus were at some point emerging diseases, that had never been observed previously in human populations but are now slowly becoming a part of the background viral infectious disease.

Following upon the development of polymerase chain reaction (PCR) and other high-throughput detection and diagnostic methods, we have seen a dramatic increase in the direct detection of viruses. New viral diseases seem to be emerging with increasing frequency by the rate of identification of new viruses. Developments in molecular and genetic epidemiology are helping us understand characteristics of pathogen. Some new viruses have been detected entirely by indirect molecular methods and named solely on the basis of genomic sequences amplified by reverse transcription and PCR. For example, identification of hepatitis C virus (HCV) stemmed directly from the application of molecular methods (1).

In particular, advances in genomics and proteomics have helped us better understand mechanisms of pathogenesis, host immunity, and have also played a pivotal role in basic research in infectious diseases. Today, an unknown virus can often be identified and sequenced within days (2). This rapid sequencing capability helps to illuminate virulence factors and pathogenic mechanisms. Molecular techniques may be crucial to the initial discovery of a new emerging virus, but classical techniques still have their place. For example, SARS-coronavirus (SARS-CoV) isolated from patients was grown in Vero cells, and when examined by electron microscopy was found to resemble a coronovirus (3). Subsequently, knowing that it was a coronovirus by electron microscopy, consensus primers were used in PCR amplification, and then genetic sequence of the virus was determined (4).

Determinants contributing to the newly emergent viruses

Many different factors can contribute to the emergence of a viral disease. These included genetic and other biological viral changes, individual and collective changes in human behavior and physical environmental changes.

The virological determinants

The international reference centers and culture collections keep track of more than 30.000 viral strains (5), and this number continues to increase. There are several genetic mechanisms that drive virus evulation. These are mutation, recombination and reassorment of genes.

Mutation

A permanent change during replication viruses in the copying process introduces mutations. When such mutations lead to new phenotyping characters that enable the virus to replicate in a new host; to replicate to a higher titer or at a faster rate, to better escape host defenses, to coincident change viral virulence, and to gain crossing the species barrier, the potential exists for emergence of a new viral disease (6).

The relatively simple structure of viruses allows mutations to occur easily. The genes of viruses (particularly RNA viruses) are prone to modifications that allow the viruses to adapt easily to new hosts. A new mutant virus can emerge in humans from among existing human viruses or from animal viruses. The potential of viruses to adapt to human hosts and the environment with relative ease, and to further evolve in virulence and transmissibility, is facilitated by rapid reproduction rates and mutation. Mutations in a nonpathogenic virus of humans can create a pathogenic virus of humans. Influenza A viruses are most dangerous to humans because of their wide host range, their rapid mutation rate, and their capacity to cause serious disease.

Pandemics occur when a new influenza virus variant emerges to which the human population has no immunity. Mutations that affect antigenic determinants on the viral surface proteins may be selected for, especially when viruses replicate in the presence of antibody. The risk of an influenza pandemic has grown as an exceptionally virulent form of the H5N1 virus and has circulated widely among domestic poultry and wild migratory birds in Asia, Europe, the Middle East, and Africa.

Genetic mutations are very common during duplication of human immunodeficiency virus (HIV) within a single cell. In time, several mutant HIV virions can be found within a single infected individual. HIV may continue to be virulent because of its fast mutation rate, recombinogenic effect, and its use of human defenses to replicate itself. Such recombination could occur in humans to produce, for example, HIV-3, because biological mechanisms that usually constrain the evolution of viruses may not apply to HIV (7).

Cross the species barrier

Viruses can emerge from animal viruses when mutation of the virus and increased accessibility to humans enables the virus to make the ‘‘cross-species jump’’ to infect humans (Table 1). The ability of animal viruses to cross the species barrier as a result of mutations has been documanted in several cases (8), but in many cases involving humans, and humans are a died-end host (9). HIV-1 and HIV-2 provide the best example of crossing the species barrier. HIV entered the human population from a simian reservoir (HIV-1 around 1931, HIV-2 around 1940) (10,11). As with many other viruses (HIV, SARS-CoV and avian influenza virus), Hendra and Nipah viruses have crossed species barriers, which have become human and animal pathogens (12, 13).

Recombination

Genetic recombination involves an interaction two or more viral genomes during mixed infection. Western equine encephalitis virus is a recombinant, its two glycoproetin genes being derived from a Sindbis-like virus progenitor and the remainder of its genome derived from Eastern equine encephalitis virus (14). That probably occurred during persistent infection in a mosquito host more than 1000 years ago (15). Recombination is also documented between serotypes of polioviruses (16).

Table 1. Examples of crossing of the species barrier

Year	Virus	Disease	Species involved
1931	HIV-1	AIDS	Chimpanzees to humans
1940	HIV-2	AIDS	Sooty Mangabies t humans
1978	Canine parvovirus	Pandemic enteritis	Cat to dog
1988	Phocid distemoper v'rus-1	Fatal respiratory disease (distemper)	Harp seals to harbor seals
1989	Phocid distemoper v'rus-2	Fatal respiratory disease (distemper)	Dogs to Siberian seals
1994	Hendra virus	Acute respiratory distress syndrome (ARDS) and encephalitis	Fruit bats to horses and humans
1999	Nipah virus	Severe respiratory disease and encephalitis	Fruit bats to pigs and humans

Reassortment

The genetic recombination during dual infections in which whole genome segments are recombined is termed reassortment. A virus of animals can mutate or recombine with a virus of humans (with reassortment of the genome, in the case of viruses with segmented genomes, such as influenza virus) to create a virus that is highly pathogenic for humans.

Different influenza A viruses can reassort their genome segments. Each of the major human influenza pandemics of 20th century (in 1918, H1N1 first appeared; in 1957, H2N2; and in 1968, H3N2 emerged) was caused by reassortment of genome segments between an existing human virus and avian virus (17). However, an antigenic shift occurs when an influenza strain emerges that is substantially different from anything to which the population has been previously exposed.

As a result of reassortment H5N1 influenza strain has emerged with the capability of infecting humans. The first documented cases of human-to-human transmission were reported in a Thai family (18). Deaths due to the H5N1 strain of avian influenza virus among poultry in Asia are considered an indication that future reassortment of this virus with the genome of human influenza virus could lead to a virulent strain emerging in humans.

Swine may provide an important intermediate host in the stabilization of reassortants between avian and human influenza viruses. Swine flu (pandemic H1N1-2009 virus infection) emerged in Mexico and Southern California (19) in April 2009 and quickly spread the globe. Triple-reassortant pandemic swine influenza viruses, which contain genes from human, swine, and avian influenza A viruses. This particular genetic combination of swine flu virus segments has not been recognized previously among swine or human isolates.

The individual host determinants

The host brings a much more complex genome to the battle between virus and host that involves the qualities

of the virus that are crucial for its transmission and survival and the resistance of the host. The host factors are; innate and acquired resistance, physiological factors affecting resistance (age, hormonal effects, nutritional status). It is known that the host immune response and physiological factors affect host resistance to viral infections.

The host population determinants

Multiple factors, including economic development and land use, human behavior, and international travel and commerce, contribute to the emergence of infectious diseases (20). For instance, changes in social structure and human behavior contributed to the emergence of HIV/AIDS. Many viral diseases are emergent depending upon individual and collective changes in human behavior. Behavioral influences include: risk factors leading to sexually transmitted diseases, behavioral risk factors associated with day care, behavioral risk factors favoring the transmission of childhood in the community, risk factors pertaining to food preparation and storage in the home, risk factors associated with keeping pet animals in the home (6).

Changes in sexual attitudes and behavior, have led to rapid amplification of certain viral diseases that are spread sexually. Children attending day care facilities may also become silent reservoir hosts for some agents of disease, such as hepatitis A virus and rotaviruses. Many viral diseases are also caused by DNA viruses with advanced medical care units (e.g. organ transplantation). Changes in every aspects of the food industry favor the emergence of new viral disease.

Social and behavioral factors include health-care procedures that facilitate the spread of infectious agents among health workers and through them into the general population. The global human population has continued to grow inexorably, bringing increasingly larger numbers of people into close contact. For this reason, viral diseases occuring anywhere in the highly mobile world can no longer be presumed to stay confined to their country or continent of origin. Globalization, with a phenomenal growth in international travel, facilitates the transfer of the infectious agents that cause emerging infectious diseases from country to country, and from continent to continent in food, animals, insects, or unsuspecting humans. Thereafter, new pathogens invade new geographic territories.

The environment (ecological and zoonotic) determinants

The human species lives in a delicate balance with microbial species, gets disturbed by land use leading to perturbations in the natural microbial environment, human demographics and behavior, international travel and commerce thus creating an imbalance and increased possibilities to trigger the emergence of new infectious diseases.

Viruses can emerge because of changes in the host, the environment, or the vector. When ecosystems are altered, viral infections of humans and animals follow. Environmental factors include naturally occurring variations in temperature and rainfall that impact on breeding sites and biting habits of insect vectors, and the modification or destruction of forests and agricultural land through economic development that modify animal, vector and human habitats. Approximately 75% of emerging pathogens are *zoonotic* (21), that is, communicated by animals to humans. HIV/AIDS, avian influenza, Nipah, SARS and Ebola are all the result of interactions with animals that led to the emergence of deadly diseases.

There are many factors influencing the epidemiology of the various zoonoses, such as population movements, human behavior, the movement of pathogens (via travel and trade), ecological changes, and arthropot vector relationship, changes in agriculture and food production, changing routes of long-distance bird migrations. The movements of pathogens, vectors, and animal hosts can occur via human travel and trade, by natural movement of wild animals including migratory birds, and by anthropogenic movements of animals. Zoonotic viruses can be transported within insects, animals, or humans to the farthest land in less time than the incubation times of most diseases.

Ecological changes of natural or human origin can have a profound impact on the epidemiology and the emergence of viral zoonoses. The opening of isolated ecosystems to human activity has contributed to the emergence of viral diseases. One classic example is the emergence of yellow fever when humans entered the Central American jungle to build the Panama Canal (22).

Changes in the habitat of the vector can lead to emergence of viruses in humans. Changes in the habitats of animal hosts such as rodents, livestock, poultry, and animals kept as pets, also can lead to viruses emerging among humans. Close contact between nonhuman primates and humans in Africa, resulting in part from habitat changes, may

have been responsible for the emergence of HIV from simian immunodeficiency virus (SIV) (23). Human disturbance and alternation of ecological zones throughout the world have increased the frequency with which microbes, usually confined to animals, cross the species barrier to infect humans. Emergence leading to outbreaks of Lassa fever in West Africa and of hantavirus in North America have been linked to such phenomena among rodents (24,25).

The henipaviruses (Hendravirus and Nipahvirus) are naturally harboured by Pteropid fruit bats (flying foxes) and a wide host range and their recent emergence as zoonotic pathogens capable of causing illness and death in domestic animals and humans (26). As there is no evidence of transmission to humans directly from bats, it is thought that human infection only occurs via an intermediate host (27). SARS-CoV, Australian bat lyssavirus, Menangle virus (28) and probably Ebola virus and Marburg virus are also harbored by bats and are capable of infecting a variety of other species. The emergence of each of these viruses has been linked to an increase in contact between bats and humans, sometimes involving an intermediate domestic animal host.

Agriculture, meatpacking, pet ownership, and hunting of animals have all enabled viruses to emerge among humans. Changing routes of long-distance bird migrations and relating to water use are becoming important factors in the emergence of viral diseases.

Conclusion

As a consequence, an impressive number of new important viruses have been recognised. Several factors such as virological (genetic mechanisms drive virus evolution), individual host and population, and environmental determinants can contribute to the emergence of a new viral disease. These determinants need to be understood for prevention and control of emerging viral diseases. Emerging infectious diseases will continue to threaten human populations in the future. Developments in molecular epidemiology are helping us understand virulence, transmission patterns, and host susceptibility. There is nearly always need for molecular epidemiological field investigation to assess the risk to the human and/or animal populations.

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