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Pathogenic viruses of the respiratory tract – A review

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ABSTRACT

Viral infections of the respiratory tract are commonly caused by viruses and millions of people are infected every year all over the world. A range of viruses are associated with the infections of the respiratory tract. Common pathogenic viruses which cause severe respiratory disorders are influenza virus, parainfluenza virus, coronavirus, respiratory syncytial virus, rhinovirus, adenovirus, metapneumovirus and enterovirus. In several studies, a specific type of virus is targeted whereas a panel of pathogenic viruses are detected in other studies. However, detection of a range of common pathogenic viruses is laborious, complicated and expensive. Technical support and skills required for the detection of a panel of respiratory viruses may not be available in many laboratories in the developing countries. Diagnosis and treatment of respiratory tract viral infections are often symptomatic and antibiotics are not recommended for such infections. This review focuses on incidence and diagnosis of pathogenic viruses associated with the infections of the respiratory tract.

1. Introduction

Respiratory tract infections caused by pathogenic viruses are reported in different seasons all over the world, which are often considered as “forgotten pandemic”[1]. Complicated cases of respiratory infections are treated in hospitals with additional medical support and uncomplicated cases account for millions of visits to family physicians and absence from work and school causing economic burden to the community[2]. Diagnosis of the pathogenic viruses is often overlooked due to the presence of heterogeneous group of viruses in the respiratory tract. Often they are mistreated with antibiotics that complicate overall treatment procedure by rising level of antibiotic resistance. Viruses can infect the upper respiratory airways causing mild infection like cold and flu. Infections can be more serious and complicated once they reach the lower respiratory system. Serious respiratory disorders may be observed in vulnerable groups such as, children, elderly and immunocompromised patients[3]. This review focuses on the previous studies on respiratory tract infections caused by different types of pathogenic viruses.

2. Respiratory tract infection

The development of molecular methods has revolutionised not only the detection of unknown viruses but also the detection of divergent novel viruses of the respiratory tract. A number of previously unknown pathogenic viruses of the respiratory tract for example, human metapneumovirus (hMPV)[4], human coronavirus (hCoV) NL63[5] and HKU1[6], Middle East respiratory syndrome coronavirus (MERS-CoV)[7], and human bocavirus (hBoV)[8] have been reported in the last two decades. Human viral infections may affect all age groups with a range of severity of infections which may depend on different environmental factors and clinical conditions[9]. Respiratory tract infections can be caused by a variety of microorganisms but the majority of such infections are caused by viruses[10]. Some of these viruses such as influenza A may cause severe disease and can lead to pandemic spread with high morbidity and mortality[11]. Other viruses such as bocavirus may cause less severe infection leading to common cold symptoms[12]. The patterns of respiratory tract infections in common cold are complex due to the potential incidence of multiple viruses in respiratory tract infections in humans.

Upper respiratory tract infections (URTI) can be caused by a wide variety of viruses, including rhinovirus, coronavirus, influenza A and B, parainfluenza, respiratory syncytial virus, adenovirus, metapneumovirus, and enterovirus; as well as by bacteria, including *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Bordetella*

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pertussis, and *Haemophilus influenzae*[13,14]. The clinical symptoms of URTI are highly variable and cannot be used to identify the aetiological agents. Traditional methods for the identification of URTI pathogens, including culture and serology are effective for many viral pathogens but are laborious and time consuming. Serological tests, for example, immunofluorescence, can be rapid but are often not sensitive or specific enough to detect all varieties of pathogenic viruses. In one study enzyme immunoassays (EIA) and direct immunofluorescence (DIF) assays showed sensitivities of 85% and 60%–80%, respectively for detection of influenza virus[15]. Although viral culture is generally accepted as the gold standard for diagnosis, PCR based detection was found to be more sensitive[16]. In another study, rhinovirus infection were detected more efficiently by PCR method (51.5%) than culture method (40%)[17]. Similarly, an influenza virus surveillance study showed better detection by TaqMan-PCR (28%) than conventional culture approach (18%)[18]. However, TaqMan-PCR is relatively expensive and is not regularly used for routine laboratory diagnosis of pathogenic viruses.

Viral infections of the respiratory tract can be self-limiting upper respiratory tract infections or more serious forms of lower respiratory tract infections. Rapid and accurate detection of pathogenic viruses of the respiratory tract can help the early diagnosis of pathogenic viral infection, decrease the duration of hospitalization and reduce management costs, as well as avoiding additional laboratory testing and unnecessary administration of antibiotics[19,20].

2.1. Global picture of respiratory tract viral infections

Respiratory tract infection is a major cause of disease burden compared to other causes of infection[21]. Respiratory tract infection is one of the leading causes of disease and results in mortality rate of 18% in children less than 5 years old. The next most common infections are diarrhoeal diseases (15%) and malaria (11%) around the world[22]. Morbidity due to respiratory tract infection in this age group varies in different parts of the world. It was reported that 22% and 26.7% of all hospitalized patients had respiratory illness in the UK[23] and Belgium[24], respectively. Amongst all other viral infections in humans, influenza was found to be associated with approximately 250 000–500 000 deaths globally each year[25]. The actual mechanism for spread of influenza seasonally worldwide is not clearly understood but is found to be associated with a number of factors including environmental conditions and patient health[26–29]. Influenza epidemics occur in the northern and southern hemispheres during their respective winters[30,31] while increased influenza activity is found to be linked to the rainy season in several tropical populations[32,33]. Other factors linked to influenza epidemics include cold temperatures[34], low indoor humidity[35] and minimal solar radiation[31]. However, a detailed study needs to be done for comprehensive description of the global pattern of seasonal activity of influenza.

3. Common pathogenic viruses associated with respiratory tract infections

Respiratory tract infections are commonly associated with a range of pathogenic viruses and clinical manifestations. There are approximately 200 known respiratory tract viruses of the

Adenoviridae, Parvoviridae, Orthomyxoviridae, Paramyxoviridae, Picornaviridae and Coronaviridae families associated with respiratory syndromes[36]. Only the common pathogenic viruses associated with respiratory tract infections are described in the following section.

3.1. Influenza virus

Human influenza viruses are enveloped, single-stranded, negative-strand, segmented RNA viruses that belong to the family Orthomyxoviridae. Influenza virus infections may lead to febrile respiratory illnesses and annual epidemics prevailing for about 3–8 weeks[37,38]. Influenza infection can spread globally in the pandemic form through the spread of novel virus types. These novel types of influenza viruses emerge following genetic reassortment of the haemagglutinin (HA) and neuraminidase (NA) genes[39].

Although three subtypes: H1N1, H2N2 and H3N2 were found to be associated with seasonal variations in the last 100 years, a new variant of H1N1 transferred from swine to humans was responsible for a pandemic (worldwide) outbreak in 2009[40]. In addition, the transfer of subtype H5N1 from birds to humans triggered the severe outbreak in Southeast Asia in 2003 and caused significant mortality and morbidity in humans[41]. Although clinicians sometimes use laboratory diagnosis, they often diagnose patients solely based on the presence of influenza-like symptoms. Identification of influenza virus in a hospital environment is important for appropriate control of the spread of infection for example, by droplet isolation. The spread of influenza infection in a hospital can be disastrous for immunocompromised patients for example, transplant recipients or cancer patients, and can cause serious complications leading to death. Transplant recipients may acquire viruses through the donor-derived infections, reactivation of endogenous latent viruses or from the community. Due to the immunocompromised states of these patients, they are susceptible to infections from any opportunistic pathogens. Administration of specific antiviral agents for example, M2 channel inhibitors (amantadine and rimantidine) can be effective in controlling the spread of infections between patients. However, for effective treatment of patients M2 channel inhibitors need to be given within first 24 h of infection. Therefore, a rapid and accurate laboratory diagnosis of influenza virus is of prime importance.

Avian influenza virus (H5N1) was first detected in Hong Kong in 1997[42] and resulted in death for 6 of 18 reported cases. A large number (1.5 million) of infected chickens were culled in Hong Kong to limit the spread of the virus from the infected chickens. Millions of wild and domestic birds were infected by H5N1 in Southeast Asia in 2003. Subsequently, 229 people died out of 359 people who became infected in 14 countries in 2008[43]. Exposure to the infected poultry caused mild to severe respiratory illness due to a new avian influenza A (H7N9) virus was initially reported in China in March 2013. However spread of such infection could not be sustained between persons[43].

3.2. Human parainfluenzavirus (PIV)

Human parainfluenza viruses are enveloped single-stranded negative-sense RNA viruses grouped within the family of Paramyxoviridae. There are four distinct serotypes of PIV associated with human infections[44,45]. The mode of transmission and

pathogenesis of PIVs are similar to those of influenza viruses. PIV1 and PIV2 are found to be the major cause of croup in children[46,47] and upper respiratory tract infection (URTI) in all other age groups[45,48]. PIV3 is more likely to be associated with severe lower respiratory tract infection (LRTI) in children. Infections caused by the PIV4 (Subtypes PIVa and PIVb) are less prevalent and less studied compared to the other common viruses of the respiratory tract[44].

3.3. Human respiratory syncytial virus (hRSV)

Human respiratory syncytial virus (hRSV) is a member of Paramyxoviridae and contains a single-stranded negative-sense RNA genome. RSV has been reported to be the major cause of bronchiolitis and pneumonia in children under the age of 2 years[49]. There are two subtypes (A and B) of hRSV found to be associated with infections caused by hRSV. There were over 100 000 hospitalization and 4500 deaths associated with hRSV infection each year in the USA, with an estimated cost to the economy of \$300 million[50].

3.4. Adenovirus

Adenoviruses are double-stranded DNA viruses of the Adenoviridae family and have more than 51 known serotypes which are categorized into six subgenera A to F. Adenoviruses can also cause other types of infections such as conjunctivitis, keratoconjunctivitis, and acute gastroenteritis. Amongst the 51 known serotypes the ones associated with the respiratory tract infections include 1–5, 7, 14, 19 and 37. Adenoviruses generally spread through inhalation of droplet nuclei and infect children under the age of 10 years old[51]. The incidence of adenovirus infections in haematopoietic stem cell transplant patients have been reported by different workers which range between 4.9% and 20.9%[52,53].

3.5. Rhinovirus

Rhinoviruses are single-stranded positive-sense RNA viruses of the Picornaviridae family of which more than 200 serotypes have been identified. Rhinoviruses cause approximately two-third of cases of common cold in humans and have been found associated with asthma exacerbations in chronic lung disease[54]. Rhinoviruses and enteroviruses belong to the same family Picornaviridae and often detected using primers specific for the highly conserved 5'-noncoding region (NCR). However, designing a second set of primers targeting the VP1 or VP4 genes can be useful to differentiate between rhinoviruses and enteroviruses. RT-PCR, nucleic acid sequence based amplification (NASBA) have been found to be more sensitive than conventional culture techniques for the detection of rhinoviruses[55].

3.6. Enterovirus and Parechovirus

Enterovirus and Parechovirus are single-stranded positive-sense RNA viruses of the Picornaviridae family. The genus *Enterovirus* and *Parechovirus* have been shown to have 63 and 4 distinct members, respectively. Enteroviruses are prevalent worldwide infecting an estimated 1 billion people each year. These infections

are common in infants and young children especially under the age of 1 year[56]. Enterovirus infections can cause a range of disease conditions starting from mild respiratory symptoms[57] to serious forms such as poliomyelitis and aseptic meningitis. Although Parechoviruses mainly cause respiratory tract and gastrointestinal infections[56] human parechoviruses can cause acute flaccid paralysis and severe encephalitis.

3.7. Human metapneumovirus

Human metapneumovirus is an RNA virus of the Paramyxoviridae family which was discovered in 2001[4]. It can cause mild to severe respiratory tract infections with symptoms very similar to those caused by hRSV and can lead to the development of bronchiolitis and pneumonia[58]. Human metapneumovirus (hMPV) can cause sporadic infection throughout the year[59] with predominant outbreaks in the winter and spring months of temperate climates[60]. This virus can spread through aerosols, droplets or contaminated surfaces and infect people of all ages primarily infants[61].

3.8. Coronavirus (CoV)

Coronaviruses are single-stranded positive-sense RNA viruses belonging to the Coronaviridae family. Of the five types of coronaviruses reported so far, HCoV-229E and NL-63 belong to Group I whereas OC43, SARS-CoV and HKU1 belong to the Group II CoVs. CoV OC43 and 229E have been found to be associated with respiratory tract infection in immunocompromised children and hospitalized elderly patients[62]. The worldwide outbreak of severe acute respiratory syndrome (SARS) from 2002 to 2003 was associated with SARS-CoV of Group II CoV.

3.9. Human bocavirus (hBoV)

Human bocavirus is a single-stranded DNA virus of the Parvoviridae family. Human bocavirus was discovered by Allander *et al.* using a large-scale molecular viral screening and DNase Sequence Independent Single Primer Amplification (SISPA) technique[8]. Based on several studies it was found that about 2%–19% of respiratory tract infections were caused by hBoV. Bocavirus infections are detected mainly by molecular techniques[63] as it is not yet possible to grow isolates in cell culture.

3.10. Parvovirus Type 4 and 5 and Mimivirus

Parvovirus type 4 and 5 were found in the serum or plasma samples of 70% of HIV infected patients[64]. Parvoviruses were also found in 4% of manufactured plasma and in healthy blood donors[65]. These types of viruses are considered as potential pathogens of the respiratory tract as are two other parvoviruses, parvovirus B19 and HBoV that are associated with respiratory tract infections.

Mimivirus is a large DNA virus considered as a potential pathogen of the respiratory tract. Antibodies to mimivirus could be detected in 9.7% of community-acquired pneumonia cases compared to 2.3% of healthy controls. Mimivirus DNA was also found in bronchoalveolar lavage specimens from intensive care unit patients[66]. However, in another study mimivirus sequence could not be detected by

real-time PCR in 496 pneumonia patients[67]. Further research is necessary in order to establish the true pathogenicity of these viruses.

4. Conclusion

Respiratory systems are dynamic and exposed to a range of microbiota like viruses, bacteria and chlamydia. Presence of viruses in the respiratory airways is especially important when they are pathogenic. Although around 200 types of viruses of different families are found to be associated with the illness of the respiratory tract all of them are not diagnosed due to the poor multiplex system for diagnosis of a range of viruses. Many of the viruses yet to be diagnosed with improved technology and devices. Future studies may be conducted for the development of new and metagenomic approaches for the diagnosis of novel viruses. It is also important to determine the economic burden of each and every pathogenic viruses. A better understanding of the epidemiology will help prevention and control of virus associated respiratory tract infections.

Conflict of interest statement

We declare that we have no conflict of interest.

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