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PATHOGENIC RESPIRATORY VIRUSES: A REVIEW

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Abstract
We studied the respiratory viruses which are unique to the lungs with their characteristics and description, which include various types such as H5N1 influenza A, influenza viruses, human metapneumovirus (HMPV), parainfluenza viruses, adenoviruses, human respiratory syncytial virus (HRSV), and picornaviruses. Also, the most widespread virus that infects the respiratory system, Coronaviruses, were discussed, with emphasis on their epidemiology, pathogenicity, clinical features, and diagnosis approaches. There are several approaches and strategies to detect respiratory viruses, which are discussed in this work. Furthermore, the importance of immunity against viral respiratory infections, which are initiated via the innate immune system and followed by adaptive immunological responses, was emphasized.

Keywords: Coronaviruses, Immunity system, Pathogenic viruses, Respiratory system, PCR.

Introduction

Respiratory infections represent a prominent death and illness source around the world. Lower respiratory disorders claimed the lives of 2.38 million individuals in the year 2016. Children under age of five and elderly accounted for the majority of mortalities. In underdeveloped nations, mortality is very high. The most prevalent causes of lower tract respiratory infections include Haemophilus influenza type b, Streptococcus pneumoniae, respiratory syncytial virus, and influenza virus (1). A viral respiratory infection occurs in the case where a virus infects respiratory mucosa cells. In the case when the particles of the virus are inhaled or come into contact with the mucosa of eyes or nose, this could take place (2). Despite the fact that bacterial pneumonia is still the leading cause of hospitalization in immunocompromised people, healthy people, and persons with comorbidities, respiratory virus infections account for a large part of the admissions to the hospital (3, 4). The development of sensitive, quick, multiplex PCR-based diagnostics allowing for broad-spectrum respiratory virus screening is crucial from a clinical standpoint. Early detection avoids unnecessary antibiotic therapy and quick isolation of infected patient, avoiding infectious agent from spreading among patients who are critically ill in the ICUs or oncohematological wards (3, 6–8).

1. Description and Features of a Virus

Viruses can be described as microscopic infectious agents made up of the genetic material (DNA or RNA) enclosed in either a protein coat (i.e. naked virus) or a lipid membrane containing glycoprotein

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spikes (enveloped virus). A virion refers to the complete infectious unit. The capsid proteins regarding both enveloped and naked viruses, along with the glycoproteins of the enveloped viruses, are key antigens for activating the host's immune response. Only living cells can replicate viruses, and their genomes include instructions for guiding the host cell to create virus-specific components needed for viral offspring development (9, 10).

2. Types of Viruses

2.1. Influenza Viruses

The influenza B, A and C virus were discovered in 1940, 1933, and 1951, respectively. The influenza B and A viruses were Orthomyxoviridae viruses, which are a subfamily of the Influenzavirus genus. Also, the influenza C virus differs from the influenza A virus in several ways. Influenza B and A are enveloped particles (encased via a cellular lipid bilayer membrane) which include a negative-sense RNA segmented genome encased via a helical capsid, with influenza B and A having 8 RNA segments and influenza C having 7 segments that code for 11 or 9 proteins (11) Clinically relevant influenza B and A are the only two strains. Influenza C infection is infrequent and normally causes a mild upper respiratory tract disease; it might cause pneumonia or bronchitis in rare cases. Neuraminidase (NA) and hemagglutinin (HA), two primary surface glycoproteins present on influenza viruses, are necessary for virion release from infected cells and virus attachment to the receptors of the host-cells, respectively. Influenza A viruses are divided into 16 HA and 9 NA sub-types depending upon the anti-genic differences in NA and HA proteins (11). Influenza B has only one kind of N and H glycoprotein. The rapid antigenic variation rate that has been induced by stepwise mutation regarding H and/or N genes, which is reflected in antigenic feature variations of such proteins (and therefore escape from the immune memory), is responsible for occurrence of the annual influenza epidemic worldwide. This is why annual vaccination of the influenza with various influenza B and A virus serotypes is essential. In addition, influenza viruses spread through droplets in the air, causing a variety of clinical symptoms that range from a mildly symptomatic infection to primary viral pneumonia that could be fatal. Influenza A viruses are more possible to result in serious illness compared to influenza C or B. Influenza A symptoms include tracheobronchitis and involvement of the small airways (12). In immunocompetent humans, virus shedding in the secretions of respiratory tract lasts 3–6 days on average, while incubation lasts days. The disease usually starts with chills, headache, and a dry cough, then progresses to a high fever, substantial myalgias, anorexia, and malaise. Otitis media, sinusitis, and bronchitis are the most common and minor influenza consequences. More serious complications, like bacterial or viral pneumonia, along with the worsening of the pre-existing diseases, are more possible to develop in young children, the elderly, persons with cardiopulmonary disorders, and people who are immunocompromised (13).

2.2. H5N1 Influenza A

New influenza viruses that have been found in Hong Kong recently, H5N1, seem to spread from the poultry to a few individuals with a high mortality rate. There is significant anxiety as avian influenza

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spreads worldwide. Hundreds of human H5NI infection cases were documented in nations worldwide, despite the fact that transmission of a strain to people is highly rare (14). The H5N1 influenza virus's capacity to develop prolonged human-to-human transmission is what keeps it from producing a pandemic with severe health and economic repercussions. Routine laboratory diagnostic tests can only tell you if you have influenza A or B, not which subtype. If needed, reference laboratories could identify the influenza strain with the use of various methods (15). The 'gold standard' method to diagnose influenza virus infection in the laboratory is the isolation of virus in the cell culture. On the other hand, this procedure is slow and it allows no prompt diagnosis and therapy. Virus isolation, on the other hand, is necessary for epidemiological studies, detecting certain influenza strains circulating in community, and detecting new strains, and therefore epidemics. The data on the strains of influenza is being utilized for the purpose of developing vaccinations for forthcoming flu season. Nasopharyngeal swabs, nasopharyngeal aspirates, lung biopsy tissue, throat swabs and sputum, and Broncho-alveolar lavages might all be used to culture influenza. All specimens must be kept at 48°C till processing. Rapid cultures have lately been produced, which entail growing influenza for up to three days before labeling cells with antibodies directed against influenza A with the use of an immunoperoxidase or fluorescence method. Those techniques are low-cost and quick, yet they necessitate a high level of technical knowledge. They can distinguish between influenza B and A, along with other viruses, yet they cannot distinguish between influenza H and A. Therefore, such tests could be insignificant throughout the early phases of an epidemic, in a case when new H type of influenza A co-circulates with old H type. Direct viral antigen detection in the respiratory samples is possible as well, which represents the recommended approach for a quick and sensitive assay. Various laboratories now have equipment that can distinguish influenza A & B viruses from other virus types using RT-PCR. In addition to that, it might help distinguish between influenza A strains H and N. The discovery of an immunological response with four-fold or larger rise in the serum antibody titers with the use of complement fixation or haemagglutination inhibition methods in convalescent and acute samples also confirms acute influenza A or B virus infection. Serological tests are uncommonly diagnostic in separate instances in time to allow for the proper utilization of the anti-influenza medications, yet they're tremendously valuable in tracking community outbreaks. IgA and IgM antibodies to influenza peak 14 days following infection, while IgG antibodies peak 4–7 weeks later. Other IgM ELISA tests could be conducted on a single sample. Because anamnestic response to the infection is maximal for strain that produced the first infection, serological testing and typing of influenza virus might be more complex. In serological assays, the so-called "doctrine of original antigenic sin" might result in a lack of strain specificity.

2.3. Parainfluenza Viruses

Human parainfluenza viruses can be categorized into four serotypes and might cause infections of upper respiratory tract in individuals of all ages (16). The viruses 4B and 4A of the parainfluenza viruses are substantially less prevalent. Parainfluenza 1–3 is the most common cause of croup in newborns and young children under the age of five. Whereas parainfluenza 3 might result

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in bronchiolitis and viral pneumonia in small children and newborns, parainfluenza 4 is very uncommon and is typically accompanied with signs of a mild upper respiratory infection (rhinorrhea, pharyngitis, and cough). In US, HPIVs are accountable around 33% of infections in the lower respiratory tract in children who are less than five year old (17, 18). The 'gold standard' for identifying parainfluenza infection in the laboratory is virus isolation in tissue culture. Parainfluenza takes 3–5 days to develop. Haemadsorption is employed for detecting such viruses since they do not cause CPE directly (adsorption of the red blood cells of the guinea pig to infected cells). Respiratory secretion samples should be maintained at 48°C till they are processed. For each kind of parainfluenza virus, rapid diagnostic approaches for viral antigen identification in respiratory samples utilizing DIF are extremely specific and sensitive. RT-PCR technologies have a high specificity and sensitivity for detecting single viruses or groups of viruses, like parainfluenza. A fourfold increase in blood anti-body levels between convalescent and acute samples collected three weeks following the beginning of acute illness can indicate infection, according to a serological response. Haemagglutination inhibition, complement fixation, and neutralization are all approaches for detecting antibodies. In specific sick persons, heterotopic antibody responses might make interpreting a serological test with regard to the type of parainfluenza that caused the infection challenging.

2.4. Human Metapneumovirus (HMPV)

In the year 2001, the human metapneumvirus (HMPV) was found in the secretions of Dutch children with bronchiotitis (19). In the elderly, small children, and immunocompromised people, HMPV might cause serious respiratory infections (20). HMPV causes lower and upper respiratory tract infections, like colds and influenza-like diseases, croup, pneumonia, bronchiolitis, and asthma and chronic obstructive pulmonary disease exacerbations, which are comparable to those caused by HRSV. HMPV has been discovered to be the 2nd or 3rd leading cause of hospitalization in young children, following HRSV and potentially influenza, in various pediatric investigations (21). The only approach of detection that is presently reliable is RT-PCR. Even though hMPV could be isolated in culture, no conventional procedures exist, and monoclonal antibodies which identify virus via DIF are being researched for clinical use. In spite of the fact that recombinant live-attenuated vaccinations that are created through the reverse genetics showed promise in the animal experiments, there are presently no licensed HMPV vaccines available (22).

2.5. Coronaviruses

Coronavirus was first isolated four decades ago in human embryonic trachea and nasal epithelium organ cultures, along with basic human kidney cell cultures (23). Four corona viruses discovered in humans cause mild respiratory infection: NL63, HKU1, OC43, and 229E. They are encased in a helical nucleocapsid that contains a 30 kb single-stranded positive-sense RNA genome, largest known autonomously replicating RNA genome (24). They are transported through the respiratory system by large droplets. Children are approximately 3 times more possible compared with the adults to get a coronavirus infection in a given year. Coronaviruses are the cause of 10%–15% of

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upper respiratory tract infections, majorly otitis media and common colds. In the previous 20 years, there were two incidences of animal betacorona viruses infecting humans, the two have led to significant illness. The first time this happened was in Guangdong, China, in 2002–2003, in the case where a new corona-virus from the genera and with origins in bats spread to human beings through intermediary host of the palm civet cats. SARS coronavirus infected 8,422 individuals, mainly in Hong Kong and China, and killed 916 of them (11% rate of mortality) (25). In 2012, the MERS-CoV, which is likewise of bat origin, infected 2494 individuals and killed 858 (a 34% fatality rate) in Saudi Arabia, using dromedary camels as an intermediate host (26).

2.5.1. Epidemiology & Pathogenesis

It is spread through huge droplets created by symptomatic patients when coughing and sneezing, yet it might also take place in asymptomatic persons and prior to the beginning of symptoms, putting people of all ages at risk (27). The nasal cavity includes larger viral loads when compared to throat, according to research, without changes in viral load between asymptomatic and symptomatic people (28). Patients can spread disease for as long as they get the symptoms and even after they have been clinically healed. A resident of the United Kingdom who had attended a conference in Singapore had infected 11 individuals when he was in a vacation in a resort in French Alps, and after that infected 11 additional people when she returned to the UK (29). Prior to settling on a surface, infected droplets could travel up to 12 meters. In ideal conditions, the virus can stay on different surfaces for several days, yet common disinfectants like hydrogen peroxide and sodium hypochlorite kill it in no more than a minute (30). Inhaling the droplets or touching the mouth, nose, or eyes after coming into contact with infected surfaces can cause infection. The virus has also been discovered in feces, and water contamination was suggested, with subsequent transmission through aerosolization/fecooral pathway (29). Trans-placental transfer from the pregnant mothers to her fetus wasn't described as far as we know. The neonatal disease that has been caused through postnatal transmission, however, is described (31). The incubation period could last between 2 and 14 days [median 5 days]. The receptor by which virus penetrates respiratory mucosa was identified in research as angiotensin receptor 2 (ACE2) (32). Different modeling studies estimate basic case reproduction rate (BCR) to be ranging between (2 and 6.47). The BCR for SARS was 2, and the BCR for the H1N1 pandemic flu was 1.3 (33).

2.5.2. Clinical Features

Cough (67.80%), sputum production (33.70%), fever (88.70%), sore throat (13.90%), exhaustion (38.10%), shortness of breath (18.70%), and headache (13.6%) have been defined as the most prevalent clinical symptoms of 2019-n-CoV infection amongst 1,099 lab-confirmed COVID-19 cases (34). A small number of COVID-19 cases had been identified (35). Vomiting (5.0%) and diarrhea (3.8%) were among the gastrointestinal symptoms displayed (33). Studies reported that ffever is the most common symptom (34). A low, mild, or even non-existent fever may be present in certain severely or critically ill people (36, 37). It was mentioned that conjunctivitis is a problem. Therefore, differentiating them from other respiratory infections might be challenging. A small number of the patients could develop

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respiratory failure, pneumonia, and mortality by the first week's end. Inflammatory cytokines like IL7, IL2, GCSF, IL10, MCP1, MIP1A, IP10, and TNF were also connected to this development (38). Acute lung injury, shock, ARDS, and acute injury of the kidney have been amongst the consequences that were noted. Recovery began in the second or third week. Those who made it out of the hospital spent an average of ten days there. Elderly patients and the ones with underlying co-morbidities are more likely to die (50–75% due to fatal cases). Adult hospitalized patients had a death rate that ranged between 4% and 11%. The total rate of the fatality cases is predicted to be ranging between 2 and 3% (33). COVID-19's first indications and symptoms are vague. In the differential diagnosis of common respiratory disorders, various infectious (influenza, adenovirus, respiratory syncytial virus [RSV], parainfluenza, HmPV) and non-infectious (dermatomyositis, vasculitis) agents must be taken into account (39).

2.5.3. Diagnosis

Up until now, the gold-standard technique for the clinical diagnoses of COVID-19 was real-time PCR detection of nucleic acids in throat and nasal swab samples or other samples of the respiratory tract, with next-generation sequencing confirming the results (40,41). Also, viruses could be discovered in feces and, in certain situations, blood. COVID-19 is not included in any of the multiplex PCR panels presently available. There are no commercially accessible tests at this time (42). Other types of laboratory examinations are often useless. In most cases, the white cell count is low or normal. Lymphoma is a dangerous disease that has been connected to lymphocyte counts of 1000 or less. The platelet count is often slightly low or normal. ESR and CRP values are usually high, although procalcitonin levels are typically low. A high level of procalcitonin could suggest presence of bacterial co-infection (42). It is impossible to overstate the significance of CT in diagnosing and evaluating COVID-19. Several patchy ground glass opacities in the bilateral, multi-focal lesions of the lung with peripheral distribution are common chest CT image findings in patients with COVID-19, while cavitation, pleural effusion, pulmonary emphysema, pericardial effusion, and thoracic lymphadenopathy are not common. CT has low rate of the missed diagnoses of COVID-19 (3.90%, 2/51) according to researches (46), and chest CT exhibited a better sensitivity compared to RT-PCR (98% versus 71%, p 0.001), suggesting that CT might be employed as one of the standard methods for COVID-19 diagnoses. CT, at the same time, is unable to differentiate between viruses or to identify specific viruses (46). Berenheim *etal.* Had discovered that 20/36 (56%) of early-stage patients had normal CT scan (47), indicating that a chest CT scan is not likely to be a reliable standalone tool for excluding COVID-19 infection, particularly in people with the early appearance of the symptoms.

2.6. Human Respiratory Syncytial Virus (HRSV)

The HRSV can be defined as a virus which causes lower and upper respiratory tract infections in humans. It belongs to Paramyxoviridae family of viruses. HRSV can be described as a single-strand negative-sense RNA virus with an RNA genome which isn't segmented and encodes many sub-genomic messenger RNAs (mRNAs). HRSV has ten sub-genomic mRNAs that code for 11 proteins: three transmembrane glycoproteins (SH, G, and F), four nucleocapsid proteins (P, N, M2-1, and L), a matrix

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M protein, two non-structural proteins (NS2 and NS1), and an RNA regulatory factor M2-2. In comparison to the HRSV, the HMPV lacks NS proteins. In infants under 6 months old, premature babies (35 months gestation), and elderly institutionalized people, HRSV is one of the prominent causes of the lower respiratory tract infections, notably pneumonia and bronchiolitis (48, 49). The presence of viral antigens or virus-specific nucleic acid sequences in the respiratory secretions can be used for diagnosing RSV infection. RSV detection is more sensitive with a nasal wash or naso-pharyngeal aspirate clinical specimen than with a nasopharyngeal swab specimen (50, 51). For HRSV detection, presently available laboratory techniques include detection of viral antigens through indirect or direct immuno-fluorescent (IF) staining (DFA/IFA) or enzyme-linked immunosorbent assays (EIA), virus isolation in tissue culture, and detections of the viral nucleic acids through amplification assays, primarily reverse transcription PCR (RT-PCR).

2.7. Adenoviruses

Adenoviruses (Ads) were initially discovered from human adenoid tissues in children in the year 1950. Ads are double-stranded DNA particles that are non-enveloped. Depending on biological features, tumorigenicity, and DNA homology, 51 human Ads serotypes were divided to 6 groups (A–F). A few Ads have a tendency for respiratory tract infection and might induce pharyngitis, coryza, tonsillitis, bronchitis, and pneumonia, among other respiratory symptoms. Up to 8% of respiratory infection cases in young children are caused by ads from sub-groups B (Ad3, 7, 14, 16, 21, 34, 35), E (Ad4) and C (Ad1, 2, 5, 6) (52). Acute respiratory diseases in the military recruits are also caused by Ad7 and Ad4 (53,54). In immunocompromised neonates and children, on the other hand, Ads are a primary cause of morbidity and death (55,56). Ad infections are usually self-limiting or minor, and they go away in two weeks with no long-term effects. Ads pneumonia has been associated to a 60% mortality rate in bone marrow transplant recipients (57). Adenoviral infection might be detected in nasopharynx, urine, and blood with the use of tissue culture or PCR (58, 59). Ads causes distinct morphological features and intra-nuclear inclusions which could be examined by light microscopy and identified via the immunohistochemistry in no more than 24 hours (60). In spite of the fact that live, enteric-coated oral Ad7 and Ad4 vaccinations efficiently decreased Ad morbidity by (95-99) %, development regarding such vaccines was halted in the year 1996. Yet, Barr Laboratories, Inc. was lately awarded a contract by the US Department of Defense for resuming production of these vaccines (61).

2.8. Picornaviruses

Picornaviruses are non-enveloped single-stranded positive-sense RNA viruses with genomes that encode a single polyprotein of 2100–2400 aa which belong to the Picornaviridae family. There are over 100 serotypes in such genus, split to 2 groups depending upon their cellular receptors.(62). This family has three genera which could lead to respiratory tract infections in humans (Enterovirus, Rhinovirus, and Parechovirus). The most common one of the causes regarding mild infections of the upper respiratory tract, like common cold, are human rhinoviruses (HRVs) (63, 64). In those with lung illness or immune problems, rhinoviruses might lead to pneumonia. Rhinoviruses were also discovered

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in middle ear fluid in 10% of sub-acute and chronic cases in which bacteria were not present, causing otitis media in the children and the infants. Exacerbations of the chronic obstructive pulmonary disease (COPD) and asthma in the adults, along with wheezing in children (64). Even though rhinovirus infection is uncommonly identified in the laboratory, RT-PCR detection of viral RNA, virus isolation, DIF detection of antigen in the cells that have been obtained from the respiratory secretions, and neutralization test or EIA detection of fourfold increase in the anti-body titres could all be done if needed. In addition, viral isolation in cell culture is highly sensitive, takes several days, and needs further antigenic characterisation with type-specific antibodies for confirming the individual rhinovirus serotype. Therefore, it's rarely employed as a diagnostic test. RT-PCR, other than as a research tool, is unlikely to become generally available. Respiratory picornaviruses have no vaccinations or particular immunoglobulins. When it's done early on in the sickness.

6. Immunity of Respiratory System

The lower respiratory tract (airways) (lungs, bronchioles, and bronchi) and the upper respiratory tract (pharynx, nasal cavity, trachea, and larynx) are the two sections of respiratory system. The immune system's hormonal and cellular responses (complement, antibodies, and antimicrobial peptides) are triggered by viral infection. The innate immune system triggers such responses by recognizing pathogens and inducing the release of pro-inflammatory chemokines and cytokines. The adaptive immune system, consisting of T cells that could directly destroy virus-infected cells and B cells that create pathogen-specific immunoglobulin on mucosal surfaces and in the serum, responds to such responses (65). Upper respiratory infections are caused by large particles becoming trapped in the sinuses and turbinates. Small particles have a chance of getting into the alveolar spaces and causing infections in lower respiratory tract (66, 67). Following entering the body, the majority of respiratory viruses, like the rhinovirus, influenza, parainfluenza virus, respiratory syncytial virus, bocavirus, meta-pneumovirus and coronavirus, might lead to local respiratory infections, while measles, Herpes, mumps, rubella, and varicella, among others, enter the body via the airways, yet spread to other organs (68).

Conclusions

1. H5N1 influenza A, Influenza viruses, HRSV, parainfluenza viruses, (HMPV), Picornaviruses, Adenoviruses, and Coronaviruses are some of the examples that cause respiratory infections.
2. Coronaviruses can infect persons of all ages via huge droplets produced through symptomatic patients' coughing and sneezing, along with people who are asymptomatic prior to symptoms arise.
3. Cough (67.80%), sputum production (33.70%), fever (88.70%), sore throat (13.90%), exhaustion (38.10%), shortness of breath (18.70%), and headache have been defined as the most prevalent clinical symptoms of 2019-nCoV infection amongst 1,099 lab-confirmed cases of COVID-19 (13.6%).
4. Nucleic acid detection via rt-PCR was the gold-standard approach for clinical diagnosis regarding COVID19 in respiratory tract samples.
5. The majority of respiratory viral infections do not have vaccines that are licensed for prevention,

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with the exception of influenza viruses.

6. The adaptive as well as the innate immune responses have been considered vital in defending the host from viral infection, according to human cell culture and animal model research.

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