"RNA Enveloped Viruses"

Paramyxoviridae

Paramyxoviridae (from Greek word para- beyond. Myxo- mucous or slime plus virus from Latin word poison). Paramyxoviridae are important class of viruses which are associated with respiratory ailments and common childhood disease such as measles and mumps, Paramyxoviridae significant cause of morbidity and mortality globally, especially in children and the elderly.

Taxonomy:

Family: Paramyxoviridae

Genus	Species
Paramyxoviruses	**Human parainfluenza virus type 1 & 3**
Rubulaviruses	**Human parainfluenza type virus 2 & 4a, 4b and Mumps virus**
Morbiliviruses	**Measles virus**
Pneumoviruses	**Respiratory syncytial virus**
Heniparvirus	**Hendravirus and Nipahvirus**

Viral Structure and Composition:

The virion is spherical, pleomorphic with particles 150 nm in diameter, helical nucleocapsid symmetry. **Envelop** of Paramyxoviridae seems to be fragile contains viral glycoproteins HN, H, G (HN= Haemagglutinin + Neuraminidase, H= Haemagglutinin only, G= none and F). **Viral genome** is single stranded RNA, linear, negative – sense and non- segmented, noninfectious about 15 kb. The negates of non- segmented genome give any opportunity for frequent genetic reassortment resulting in the fact that all members of the Paramyxoviridae group are genetically stable. **Replication** events occur in the cytoplasm and particles bud from plasma membrane.

Most Paramyxoviridae contain six **structural proteins**, three are complexes with viral RNA: (N) nucleoprotein that forms the helical nucleopsid and two other large proteins (designated P and L) which are involved in the viral polymerase activity that functions in transcription and RNA replication. Three proteins participate in the formation of the viral envelop. A matrix (M) protein underlies the viral envelope the activities of these surface glycoproteins help differentiates the various genera of the Paramyxoviridae family.

The larger glycoprotein HN or G responsible for attachment to the host cell. The other glycoprotein (E) mediates membrane fusion and hemolysin activities. The pneumoviruses and contain two additional small envelope proteins (M2-1 and SH).

Replication Cycle:

The typical Paramyxoviridae replication cycle is illustrated as follow:

Adsorption and Penetration:

The H(N)/ G protein recognizes receptors on cell surface. The F protein facilitates fusion between membrane at physiological pH, although paramyxoviridae can be taken up by endocytosis, they also often enter the cell by direct fusion with plasma membrane. Because the F protein functions at physiological pH this can result in syncytia being formed in paramyxoviruses infection.

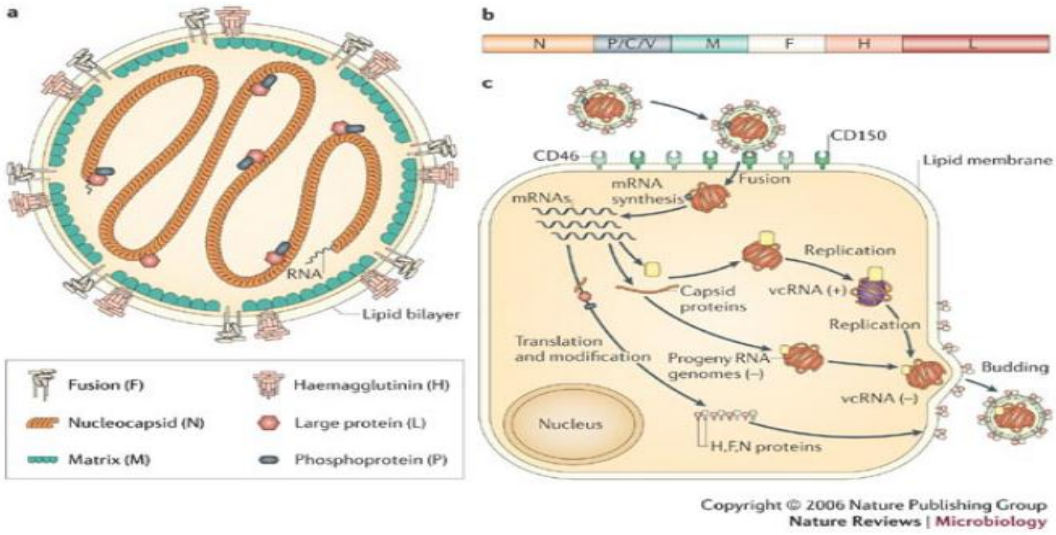
Transcription, Translation and Replication of RNA:

Events inside the cell involve:

- Viral multiplication occur in the cytoplasm
- The viral RNA polymerases uses the nucleocapsid as template
- Viral mRNAs are transcribed, these are capped, methylated and polyadenylated
- Since this is a negative- strand RNA viruses are RNA polymerase and RNA modification enzymes and packaged in the virion
- The viral mRNAs are translated to give viral proteins.
  So, viral replication involves full length strands are coated with nucleocapsid protein as they are made. New full length minus strands may serve as template for replication or template for transcription or they may be packaged into new virions.

Assembly:

Both viral glycoproteins (attachment and fusion proteins) are translated as trans membrane proteins and transported to the cell membrane. M (matrix) protein enables nucleocapsid to interact with the regions of the plasma membrane which have the glycoproteins inserted. The virus buds out through membrane.



"Replication cycle"

Human Parainfluenza viruses (HPIV)

Parainfluenza viruses are ubiquitous and cause common respiratory illnesses in person of all ages. These are major pathogens of sever respiratory tract disease in infants and young children.

Pathogenesis:

The infection may involve only the nose and throat, resulting in harmless "common cold syndrome". Infection may be more extensive especially with type 1 and 2 may involve the larynx and upper trachea resulting in croup (laryngotracheobronchitis). Croup is characterized by respiratory obstruction due to swelling of the larynx and related structure. The infection may spread deeper to the lower trachea and bronchi, culminating in pneumonia especially type 3.
Duration of Parainfluenza virus shedding about 1 week after onset of illness. The production of virus specific IgE antibodies during primary infections has been associated with disease severity. The mechanism may be also involving release of some mediators of inflammation.

Clinical findings: Parainfluenza viruses are transmitted by direct person to person contact or by large droplet aerosols. HPI-1 is the leading cause of croup in children, HPIV-2 also causes croup in children but doctors detect it much less often than HPIV-1. It's seen mostly in autumn but to a lesser degree than HPIV-1. An infection by HPIV-3 is mostly associated with pneumonia and bronchiolitis. Common symptoms of the four types of HPIV are very similar to those of the common cold, they include:-

- ✓ Fever
- ✓ Cough
- ✓ Runny nose
- ✓ Chest pain
- ✓ Sore throat
- ✓ Shortness and difficulty breathing
- ✓ Wheezing.

Laboratory Diagnosis:

Samples: Nasal swabs and Bronchoalveolar lavage fluid.

A- Isolation of virus: a continuous monkey kidney cell lines LLC-MK2 is suitable for isolation of Parainfluenza viruses, parainfluenza viruses grow slowly and produce very little cytopathic effect.

B- Nucleic acid detection: RT-PCR assays are a sensitive method.

C- Serology: Direct and indirect immunofluorescence tests, neutralization test and ELISA test for measuring antibodies level.

Prevention and treatment:
Supportive: Fluids, oxygen, respiratory support.
Antiviral agents: Ribavirin, a synthetic guanosine analogue given as aerosol.
Prevention spread: Hand washing, disinfectants of surfaces, gloves, masks.
Prevention of disease: involve active immunization (formalin inactivated vaccine), pooled hyper immune globulin and monoclonal antibody F protein.

Respiratory Syncytial virus

Respiratory syncytial virus is the most important cause of lower respiratory illness in infants and young children, usually outranking all other microbial pathogens as the cause of bronchiolitis and pneumonia in infants under 1 year of age. It is estimated to account for approximately 25% of pediatric hospitalizations due to respiratory disease.

Pathogenesis and immunity:
The incubation period between exposure and onset of illness is 3-5 days. Viral shedding may persist for 1-3 weeks in infants and young children, whereas adults shed for only 1-2 days. RSV occurs initially in epithelial cells of the nasopharynx, virus may spread into the lower respiratory tract and cause bronchiolitis and pneumonia (1/2 of cases lead to bronchiolitis and 1/4 of cases lead to pneumonia in infants).
An intact immune system seems to be important in resolving an infection, as patients with impaired cell mediated immunity may become persistently infected with respiratory syncytial virus although the airways of very young infants are narrow and more radially obstructed by inflammation and edema, a subset of young babies develops sever respiratory syncytial virus disease. High levels of neutralizing antibody that is maternally transmitted and present during the first several months of life are believed to be critical in protective immunity against lower respiratory tract illness. RSV is not an effective inducer of interferon in contrast to Influenza and Parainfluenza virus infections. Younger infants have IgG and IgA secretory antibodies responses to RSV than do other infants. An association has been noted between virus- specific IgE antibody and severity of disease. Viral secretory IgE antibodies have been correlated with occurrence of bronchiolitis.
Symptoms:
Symptoms vary and differ with age, older children usually have only mild, cold like- syndrome such as croup cough. Infants under age 1 may have more sever symptoms and often have the most trouble breathing.

- ✓ Bluish skin color due to cyanosis in sever cases
- ✓ Breathing difficulty
- ✓ Nasal flaring
- ✓ Rapid and shortness of breath
- ✓ Wheezing

  So, a breathing machine (ventilator) may be needed

Mumps virus

Mumps is an acute contagious disease characterized by non- suppurate enlargement of salivary glands, also known as epidemic parotitis. Mumps virus mostly causes a mild childhood disease but in adults complications including meningitis and orchitis are fairly common. More than one-third of all mumps infections are asymptomatic.

Mumps is highly contagious and spread rapidly among people living in close quarters, the virus is transmitted by respiratory droplets or direct contact with an infected person. Human are the only natural host for mumps virus.

Pathogenesis:

Incubation period may range from 2-4 weeks, symptoms typically occur 16- 18 days after exposure and resolve after 7 to 10 days and symptoms in adults are often more sever than in children. Primary replication occurs in nasal or upper respiratory tract epithelial cells, viremia then disseminates the virus to the salivary glands involve the parotid gland. Mumps is a systemic viral disease with a propensity to replicate in epithelial cells in various visceral organs. Virus frequently infects the kidneys and CNS, so complications may include infection of the covering of the brain, pancreatitis, permanent deafness and painful testicular swelling which results in infertility. Women may develop ovarian swelling but this does not increase the risk of infertility.

Symptoms usually appear about two to three weeks after exposure to the virus and may include:

- ✓ swollen painful salivary glands on one or both sides of face (parotitis)
- ✓ fever
- ✓ headache
- ✓ muscle aches
- ✓ weakness and fatigue
- ✓ loss of appetite
- ✓ pain while chewing or swelling

The primary and best known sign of mumps is swollen salivary glands that cause the cheeks to puff out. The term mumps "is an old expression for lumps or bumps of cheeks".

Laboratory Diagnosis:

The diagnosis of typical cases usually can be made on the basis of clinical findings, however in cases without parotitis the laboratory diagnosis can be helpful in the diagnosis involve viral isolation from saliva and CSF using monkey kidney cell. Reverse transcriptase- PCR technique can be used to detect the virus strains in clinical samples.

Prevention and Control:

Mumps vaccine is available in combination with Measles and Rubella (MMR) live- virus attenuated vaccine. Two doses of MMR are recommended for school entry. There is no specific therapy.

Measles virus

Measles also known as morbili, rubeola or red measles. It is a highly contagious infection caused by measles virus.

Pathogenesis:

Human are the only natural hosts for measles virus. The virus gains access to the human body via the respiratory tract where multiply locally, the infection spreads then to the regional lymphoid tissue where further multiplication occurs. Primary viremia disseminated the virus which can replicate in the reticuloendothelial system, a secondary viremia seeds the epithelial surfaces of the body including skin, respiratory tract and conjunctiva where replication occurs. Measles can replicate in certain lymphocytes. Multinucleated giant cells with intranuclear inclusion are seen in lymphoid tissues throughout the body (lymph node, tonsils and appendix). The characteristic of maculopapular rash appears about day 14. The rash develops as a result of interaction of immune T- cell with virus infected cells in the small blood vessels.

Involvement of the central nervous system is common in measles. Symptomatic encephalitis develops in about 1: 1000 cases. A rare late complication of measles is subacute sclerosing panencephalitis (SSPE) develops years after the infection. Measles signs and symptoms appear 10-14 days after exposure to the virus. Signs and symptoms of measles typically include:

- ✓ fever
- ✓ dry cough
- ✓ runny nose
- ✓ sore throat
- ✓ inflamed eyes (conjunctivitis)
- ✓ tiny, white spots with bluish- white centers on a red background found inside the mouth on the inner lining of the cheek also called koplik's spots.
- ✓ A skin rash made up of large, flat blotches that often flow into one another.

Laboratory Diagnosis:

Typical measles is reliably diagnosed on clinical grounds, laboratory diagnosis may be necessary in the diagnosis of a typical measles.

A-Nucleic acid detection: viral RNA can be detecting by RT-PCR, it is a sensitive method.

B-Isolation and identification of virus: nasopharyngeal, conjunctiva swabs, blood samples, respiratory secretions and urine are appropriate source for viral isolation. Monkey or human kidney cells or a lymphoblastoid cell line B95-a are optimal for isolation attempts, measles virus grows slowly, typical cytopathic effects (multinucleated giant cells containing both intranuclear and intracytoplasmic inclusion bodies) take 7 to 10 days to develop.

B- Serology: ELISA and neutralization tests all may be used to measure measles antibodies, ELISA is the most practical method.

Rubella (German measles) virus

Rubella (German measles, 3- days measles) is an acute febrile illness characterized by a rash and lymphadenopathy that affects children and young adults. It is the mildest of common viral exanthema. There are two types of rubella infection postnatal and congenital rubella infections.

Postnatal rubella:

Neonatal, childhood and adult infections occur through the mucosa of the upper respiratory tract. Incubation period about 12 days or longer, initial viral replication probably occurs in the respiratory tract followed by multiplication in the cervical lymph nodes. Viremia develops after 7-9 days. Rubella usually begins with malaise, low grade fever and morbilliform rash appearing on the same day. The rash start on the face extends over the trunk and extremities. Transient arthralgia and arthritis are commonly seen in adults, especially women but rubella arthritis is not etiologically related to rheumatoid arthritis. Rare complication includes thrombocytopenic purpura and encephalitis. IgM rubella antibodies found in a single serum sample obtained 2 weeks after the rash and IgG rubella antibodies usually persist for life.

Congenital rubella:

Maternal viremia associated with rubella infection during pregnancy may result in infection of the placenta and fetus. Only eliminated number of fetal cells becomes infected. The presence of rubella virus in uterus lead to fetal birth, birth defect or live birth and the effect is either transient in infant involve growth retardation, thrombocytopenia puerperal, hepatospleenomegally, otitis and failure to thrive. Permanent manifestation appear at birth may lead to congenital heart disease, total or partial blindness and total or partial deafness.

Laboratory Diagnosis:

A-Isolation and identification of virus: nasopharyngeal or throat swabs a good source of rubella virus. Various cell lines of monkey or rabbit origin may be used.

B- Nucleic acid detection: RT-PCR can be used and throat swabs are appropriate samples for molecular typing.

C-Serology: HI and ELISA can be adapted for detecting specific IgM and IgG, as there is only one serotypes of rubella virus.

Prevention and control:

Attenuated live rubella vaccine according to vaccination policy can be used, (MMR) give to boy and girls at 13-15 months, boys before entering the school (4-5 years) and girls at (10-14 years old in a single dose).