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Chapter 59 Paramyxoviruses

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General Concepts

Paramyxoviruses

The family **Paramyxoviridae** consists of three genera: *Paramyxovirus*, which includes the **parainfluenza** viruses and mumps virus; *Pneumovirus*, which includes respiratory syncytial virus; and *Morbillivirus*, which includes the measles virus.

Structure

All paramyxoviruses are enveloped particles 150 to 300 nm in diameter. The tubelike, helically symmetrical nucleocapsid contains a monopartite, single-stranded, negative-sense RNA genome and an RNA-directed RNA polymerase. The nucleocapsid associates with the matrix protein (M) at the base of a double-layered lipid envelope. The spikes on the envelope contain two glycoproteins, a viral attachment protein, and a fusion protein. The paramyxoviruses can be distinguished by the gene order for the viral proteins and by the biochemical properties for their viral attachment proteins. In **parainfluenza** viruses, the viral protein spikes have hemagglutinating and neuraminidase activities (HN). Respiratory syncytial virus lacks both these activities and measles virus lacks neuraminidase but has hemagglutinating activity. All paramyxoviruses are labile to very labile and quickly inactivated, e.g. by heat, organic solvents, detergents, ultraviolet, or visible light, and low pH value.

Multiplication

The multiplication of all paramyxoviruses is similar to that of orthomyxoviruses except that the paramyxovirus genome is monopartite.

Parainfluenza Viruses

Clinical Manifestations

Parainfluenza viruses cause mild or severe upper and lower respiratory tract **infections**, particularly in children.

Classification and Antigenic Types

Human **parainfluenza** viruses are divided into types 1, 2, 3, and 4; type 4 consists of A and B subtypes.

Pathogenesis

Transmission is by droplets or direct contact. The virus disseminates locally in the ciliated epithelial cells of the respiratory mucosa.

Host Defenses

Nonspecific defenses, including interferon, are followed by the appearance of secretory and humoral antibodies and cell-mediated immune responses.

Epidemiology

Parainfluenza virus diseases occur worldwide; they are usually endemic but sometimes epidemic. Primary **infections** occur in young children; reinfection is common but results in milder disease.

Diagnosis

Clinical symptoms are nonspecific. Laboratory diagnosis is made by detecting viral antigen, by isolating the virus, or by detecting a rise in antibody titer or elevated IgG- and IgA- (IgM-) antibodies in a single serum.

Control

No vaccine is available.

Respiratory Syncytial Virus

Clinical Manifestations

This virus causes upper and lower respiratory tract disease; the latter is most frequent in young children and is also significant in the elderly.

Classification and Antigenic Types

Respiratory syncytial viruses are divided into types A and B.

Pathogenesis

Transmission is by droplets or direct contact. The virus infects the ciliated epithelial cells of the respiratory mucosa and disseminates locally. Disease is caused partly by immunopathologic antibody-dependent cellular cytotoxicity.

Host Defenses

Nonspecific immune defenses, including interferon, are followed by the appearance of secretory and serum antibody and cell-mediated responses. Reinfection occurs, but the frequency and severity of disease decrease with age.

Epidemiology

This disease is found worldwide; in temperate climates, epidemics occur in winter and early spring and affect mainly infants and young children.

Diagnosis

Clinical symptoms are nonspecific; laboratory diagnosis is made by detecting viral antigen, by isolating the virus or by detecting RNA with polymerase chain reaction (PCR), or by detecting a rise in antibody titer or elevated IgM antibodies in a single serum.

Control

There is no vaccine. Aerosolized ribavirin can be used for treatment if necessary. In hospital wards, infected patients may be isolated.

Mumps Virus

Clinical Manifestations

Mumps is a systemic febrile infection of children and young adults. Swelling of the salivary glands, especially the parotid glands, is characteristic; meningitis is common; and pancreatitis, encephalitis, and hearing loss may occur. In young adults, orchitis or oophoritis is not uncommon.

Classification and Antigenic Type

The single serotype of mumps virus shares antigens with **parainfluenza** viruses, particularly type 1.

Pathogenesis

The virus is spread in droplets. Primary infection consists of viremia and involvement of glandular and nervous tissue, resulting in inflammation and cell death.

Host Defenses

Interferon and other initial defenses are followed by specific cellular and humoral immune responses, which confer lifelong immunity.

Epidemiology

Mumps is found worldwide. Without extensive vaccination it is endemic in cities with epidemic variations in 2 to 3 years intervals. In rural areas it is intermittent, reappearing there every 5 to 7 years, and may reach epidemic proportions. In temperate climates, the incidence peaks from January to May.

Diagnosis

In typical cases, the clinical picture is diagnostic. Atypical cases are diagnosed by isolating the virus in cell culture, or by detecting viral antigen or RNA, and most easily by detecting specific IgM in the first serum sample soon after onset of symptoms or by a rise of IgG antibodies.

Control

Vaccination with live attenuated mumps virus vaccine gives long-lasting immunity, but reinfection may occur

Measles Virus

Clinical Manifestations

Measles sets in abruptly with coryza, conjunctivitis, fever, and rash. The typical maculopapular rash appears 1 to 3 days later. Complications include otitis, pneumonia, and encephalitis. Subacute sclerosing panencephalitis is a rare late sequela.

Classification and Antigenic Type

There is only a single antigenic type.

Pathogenesis

The virus causes viremia with wide dissemination and multiplies in cells of the lymphatic, respiratory, intestinal and urinary system, the skin, and sometimes the brain.

Host Defenses

Interferon and other initial defenses are followed by specific cellular and humoral immune responses, which confer long-lasting immunity.

Epidemiology

Prior to the vaccine era measles occurred worldwide in an endemic or epidemic pattern and disease was inevitable. In temperate climates, the incidence peaks in the late winter and early summer.

Diagnosis

In typical cases, the clinical picture is diagnostic. Atypical cases or cases following previous vaccination are diagnosed by isolating the virus in cell culture by direct smear of cell-containing specimen, by detection of RNA with the polymerase chain reaction (Rt-PCR) or detecting specific IgM in the first serum at the time of rash with a rising titer of IgG antibodies in the second serum.

Control

Active vaccination with a live attenuated virus vaccine gives long-lasting protection. Passive prophylaxis with measles immunoglobulin is used to prevent disease in susceptible, exposed individuals.

Introduction

The family **Paramyxoviridae** consists of three genera: *Paramyxovirus, Pneumovirus*, and *Morbillivirus* (Table 59-1). All members of the genus *Paramyxovirus* share similar properties. Pneumoviruses lack hemagglutinin and neuraminidase activity. They also differ from other paramyxoviruses in morphology (diameter of nucleocapsid and surface projections). *Morbillivirus* is distinguished by the absence of neuraminidase in the virions and by the presence of common envelope and nucleocapsid antigens in the species listed in Table 59-1.

Parainfluenza Viruses

Clinical Manifestations

Parainfluenza viruses cause approximately 30 to 40 percent of all acute respiratory **infections** in infants and children. The spectrum of disease ranges from a mild, febrile common cold to severe, potentially life-threatening croup, bronchiolitis, and pneumonia. Types 1 to 3 are the most common identifiable agents of croup and are surpassed only by respiratory syncytial virus as the cause of severe lower respiratory tract disease in infants. Reinfection, causing milder upper respiratory illness, is common in older children and adults. Type 4 causes usually only mild upper respiratory infection in children and adults, but severe symptoms can occur in infants.

Structure

The virions are enveloped particles with an average diameter of 120 to 300 nm. The complete virion consists of a nucleocapsid and an envelope (Fig. 59-1). The 12-18-nm-wide nucleocapsid is a tubelike structure with helical symmetry. It contains one molecule of single-stranded generally negative-sense RNA (molecular weight 5-8 $\times$ 10^6), the major nucleoprotein (NP), the phosphoprotein P and the L protein. The L protein is the RNA polymerase which is necessary for transcription of viral RNA. The P protein facilitates RNA synthesis and the NP protein helps to maintain genome structure. The envelope is a double-layered membrane covered with spikes. It contains lipoproteins and glycoproteins, as well as lipids derived mainly from the host cell. The nonglycosylated matrix protein (M) is attached to the inner side of the envelope, the two glycoproteins that form the spikes contain the hemagglutinin and neuraminidase (HN) and the cell fusion protein (F), which is activated by proteolytic cleavage**.**

Classification and Antigenic Types

Among the paramyxoviruses four human **parainfluenza** serotypes are now recognized: 1, 2, 3, and 4. Type 4 occurs in two subtypes (A and B), which possess common internal but different capsid antigens.

Multiplication

Parainfluenza viruses attach to the host cell by the hemagglutinin, which binds to the host cell neuraminic acid receptor, and then penetrate the cell by fusion with the cell membrane mediated by the F_1 and F_2 glycopeptides. The viral particles contain single-stranded negative-sense RNA, which cannot serve as a messenger. The virion transcriptase initiates transcription into 5-8 complementary messenger positive-sense RNA strands. They direct the viral protein synthesis and are copied into negative-sense RNA strands which are integrated in the new virions. For envelopment, the virus-specific glycoproteins accumulate in the cell membrane. Assembly is completed by budding of the nucleocapsid through the cell membrane studded with glycoproteins.

Pathogenesis

The **parainfluenza** viruses generally initiate localized **infections** in the upper and lower respiratory tracts without causing systemic infection (Fig. 59-2), although viremia may occur. Local and serum antibodies develop after primary infection. The resulting immunity is not adequate to prevent reinfection, but does provide some protection against disease.

These viruses first infect the ciliated epithelial cells of the nose and throat. Infection may extend to the paranasal sinuses, the middle ear, and occasionally to the lower respiratory tract. Progeny viruses spread among cells both extracellularly and intracellularly. Virus is shed in the respiratory secretions for 3 to 16 days following primary infection and for 1 to 4 days following reinfection**.** Shedding starts shortly before the onset of disease and ends with development of local antibody. The main pathogenic change is an inflammatory response in the superficial layers of the mucous membranes.

The most characteristic and important clinical syndromes associated with **parainfluenza** virus infection are croup, bronchiolitis, and pneumonia. The development of croup is linked to IgE antibodies and the release of histamine. The most severe manifestation of infection with types 1 and 2 viruses is croup, whereas type 3 virus causes all three syndromes. **Parainfluenza** type 3 can also cause meningitis. Type 4 **infections** usually cause mild symptoms but cases with symptoms of bronchiolitis, pneumonia or aseptic meningitis have been reported. **Parainfluenza** virus infection with all 4 types can cause serious illness in immunosuppressed individuals**.**Croup caused by **parainfluenza** virus is not distinguishable from that caused by other viruses such as respiratory syncytial virus or measles virus.

Host Defenses

Nonspecific defenses (including interferon) may contribute to resistance against human **parainfluenza** viruses. The immunologic events during and after natural infection with **parainfluenza** viruses in infants and children are not well understood. Type-specific secretory and humoral immune responses occur, but protection does not last, since reinfection with the same serotype may occur within 3 months to several years after primary infection. The degree of resistance to reinfection and, even more, to clinical disease seems to depend mainly on the concentration of secretory IgA antibodies that possess neutralizing activity. Neutralizing IgA is found in infants and young children only for a short time after primary infection. Serum antibodies usually are not significant in resistance to reinfection with the nonsystemic respiratory viruses, but their presence in high titers may restrict local virus multiplication and disease manifestation. Passive maternal antibodies do not totally protect against infection; however they appear to influence disease manifestations with types 1 and 2 virus**.** Also maternal antibodies may suppress the immune response following primary infection.

Epidemiology

The **parainfluenza** viruses are distributed worldwide, causing infection and illness in young children. These virus **infections** are endemic, sometimes reaching epidemic proportions. **Infections** with **parainfluenza** virus types 1 and 2 peak in the winter months, whereas **parainfluenza** virus type 3 appears throughout the year. The source of human **parainfluenza** virus infection is the respiratory tract of humans; the incubation period ranges from 2 to 6 (to 10) days**.**In primary infection virus is shed in the respiratory secretions for 3 to 16 days and 1 to 4 days following reinfection. **Parainfluenza** viruses are transmitted by direct person-to-person contact and by the airborne route through large droplets. Only a small inoculum is required to infect. However, **parainfluenza** viruses are labile and do not persist in the environment. They are spread mainly by infants and preschool children with only mild signs of infection.

Diagnosis

Diagnosis based on clinical manifestations is not possible. Laboratory diagnosis is made by detection of viral antigens by fluorescent-antibody staining of nasopharyngeal cells or the enzyme-linked immunosorbent assay in sonicated nasopharyngeal specimens. A reverse transcription PCR enzyme immunoassay is available for rapid detection of **parainfluenza** type 3 RNA in respiratory specimens.

Serologic evidence of infection may be obtained by demonstrating a significant rise in antibody titer between two serum samples. Serodiagnosis by this means is clouded by the heterotypic anamnestic responses to previous **parainfluenza** infection. An early and usually reliable serodiagnosis of infection can be made by the demonstration of significant levels of IgA or IgM antibodies in a single-serum sample. **Infections** are not always recognizable serologically due to the insufficient induction of antibodies.

Control

Cross-infection with **parainfluenza** virus types 1 and 3 is common in hospital wards and day care centers. It can be prevented by strict isolation. Recent techniques that allow rapid diagnosis facilitate such control.

Active immunization against **parainfluenza** viruses is desirable but not yet available. Experimental killed vaccines are not effective. A live attenuated bovine para influenza virus type 3 vaccine seems to be safe, infectious, immunogenic and phenotypical stable in infants and children. Passive prophylaxis with human immunoglobulin in exposed infants is not indicated, because it may dampen an active serum antibody response. Ribavirin may be effective but it also has toxic side effects.

Respiratory Syncytial Virus

Clinical Manifestations

Most respiratory syncytial virus **infections** lead to illnesses ranging from mild upper respiratory disease to life-threatening lower respiratory tract illness (e.g., bronchiolitis and pneumonitis) in infants and young children, among whom respiratory syncytial virus is the most important serious lower respiratory tract pathogen. It is also an important cause of otitis media in young children. It can infect the middle ear directly or predispose individuals to bacterial superinfection. Older children and adults usually have common cold symptoms. In the elderly patients, respiratory syncytial virus can again be a significant lower respiratory tract pathogen.

Morbidity and mortality are greatest in the very young infants (less than 6 months of age, in preterm infants with underlying pulmonary or cardiac disease and in immunodeficient children.

Structure

Respiratory syncytial virus has a linear single-stranded RNA of about 5×10^6 daltons, which encodes at least 10 proteins (7-8 structural and 2 nonstructural proteins). The RNA is surrounded by a helical nucleocapsid, which in turn is surrounded by an envelope of pleomorphic structure. Virions range from 120 to 300 nm in diameter. Protective antibody appears to be evoked only by the F and G protein, F elicits a cell mediated as well as a humoral response. Respiratory syncytial virus has neither hemagglutinin nor neuraminidase activity.

Classification and Antigenic Types

Respiratory syncytial virus belongs to a separate genus, *Pneumovirus*, because of its distinctive surface projections, nucleocapsid diameter, molecular weight of the N and P proteins, lack of hemagglutinin and neuraminidase activity, and differences in number and order of its genes. RSV is divided in two subgroups A and B based on the G protein antigen.

Multiplication

After absorption, penetration, and uncoating, the respiratory syncytial virus genome serves as a template for the production of 10 different mRNA species and a full-length, positive-sense complementary RNA (cRNA). The mRNAs serve as the template for translation of viral proteins. The full-length, cRNA serves as a template for transcription of virion RNA. Within 10 to 24 h after infection, projections of viral proteins appear on the cell surface, and virions bud through the cell membrane incorporating part of the cell membrane into their envelope.

Pathogenesis

Respiratory syncytial virus generally initiates a localized infection in the upper or lower respiratory tract or both (Fig. 59-2). The degree of illness varies with the age and immune status of the host.

Initially, the virus infects the ciliated mucosal epithelial cells of the nose, eyes, and mouth. Infection generally is confined to the epithelium of the upper respiratory tract, but may involve the lower respiratory tract. The virus spreads both extracellularly and by fusion of cells to form syncytia. Thus, humoral antibodies that do not penetrate intracellularly cannot completely restrict infection. The virus is shed in respiratory secretions usually for about 5 days and sometimes for as long as 3 weeks. Shedding begins with the onset of symptoms and declines with the appearance of local antibody.

The most important clinical syndromes caused by respiratory syncytial virus are bronchiolitis and pneumonia in infants, croup and tracheobronchitis in young children, and tracheobronchitis and pneumonia in the elderly. Conjunctivitis, otitis media, and various exanthems involving the trunk or face, or both, are occasionally seen in primary and secondary **infections**.

Bronchiolitis is inflammatory, and pneumonia is interstitial. The pathogenesis of bronchiolitis may be immunologic or directly due to viral cytopathology. Respiratory syncytial virus bronchiolitis during the first year of life may be a risk factor for the later development of asthma and sensitization to common allergens.

Host Defenses

Nonspecific defenses such as virus-inhibitory substances in secretions probably contribute to resistance to and recovery from respiratory syncytial virus infection. Age, immunologic competence, and physical condition also appear to be important. Data on the development, persistence, and effectiveness of specific cell-mediated and secretory immunity in first and repeat **infections** are still fragmentary. Although secretory and serum antibody responses occur, immunity does not protect completely against reinfection and repeat illness, which may occur as early as a few weeks after recovery from the first infection. Protective immunity is mainly elicited by the F and G proteins.

Resistance to reinfection and repeat illness seems to depend mainly on the presence of neutralizing antibody activity on the mucosal surfaces. There is increasing evidence that humoral antibody contributes to protection from lower but not upper respiratory tract infection.

Epidemiology

Respiratory syncytial virus is distributed worldwide, causing infection and illness in infants and young children. The infection is endemic, reaching epidemic proportions every year. In temperate climates, these epidemics occur each winter and last 4 to 5 months, with peaks mainly from January to March. Both RSV subgroups A and B circulate during these epidemics. Estimates for urban settings suggest that about one-half of the susceptible infants undergo primary infection in each epidemic. The infection is almost universal by the second birthday. Reinfection may occur as early as a few weeks after recovery, but usually takes place during subsequent annual outbreaks, with a rate of 10 to 20 percent per epidemic throughout childhood. In adults, the frequency of reinfection is lower.

The source of human respiratory syncytial virus infection is the respiratory tract of humans. The incubation period for the disease is about 4 days. As noted above, primary **infections** are contagious from about 5 days to 3 weeks, with greatest virus shedding in the first 4 to 5 days after onset of symptoms. The contagious periods become progressively shorter during reinfections. The virus is transmitted by direct person-to-person contact and by the airborne route through droplet spread. It is probably introduced into families by schoolchildren undergoing reinfection. Secondary spread is to younger siblings and parents. In hospital and institutional settings, mildly symptomatic infected adults also spread the infection. Respiratory syncytial virus readily infects infants during the first few months of life despite the presence of maternal serum antibodies. Thus, the age at which first infection takes place depends primarily on the opportunity for exposure. Sex and socioeconomic factors appear also to influence the outcome of infection.

Diagnosis

In infants with lower respiratory tract disease, respiratory syncytial virus infection can be strongly suspected on the basis of the time of year, the presence of a typical outbreak, and the family epidemiology. Aside from this virus, only **parainfluenza** virus type 3 attacks infants with any frequency during the first few months of life.

Definite diagnosis of infection (of practical importance in ruling out bacterial involvement) rests on the virology laboratory. Rapid diagnosis can be made within hours by using fluorescent antibody staining of infected nasal epithelial cells or by antigen detection in the nasopharyngeal secretion by enzyme-linked immunosorbent assay and by detecting viral RNA polymerase chain reaction (PCR). Isolation of virus in various types of cell culture takes 3-6 days for recognition of the characteristic cytopathic effect. Serologic diagnosis can be made by detecting a significant rise of antibody in 2-3 weeks or by detecting specific IgM antibodies in a single serum.

Serological response in young infants following primary infection may be poor. After repeated infection an

anamnestic response generally occurs.

Control

It is nearly impossible to prevent respiratory syncytial virus transmission in the home setting. In hospital wards, cross-infection may be restricted by isolation and sanitation. Despite its tremendous clinical and economic impact, therapy and prevention of respiratory syncytial virus illness remains problematic. As yet, there is no safe and effective vaccine against RSV.

A promising means of protection is the administration of RSV-enriched polyclonal immunoglobulin (RSVIG) with monthly high-dose infusion. The maintenance of high-titer RSV neutralizing antibodies seems to significantly decrease the incidence and severity of respiratory syncytial virus illness in children at high risk.

The only approved antiviral agent for the treatment of RSV illness, e.g. in the USA, is ribavirin. It has been in use since 1986. However, the safety and clinical efficacy remain controversial.

Mumps Virus

Clinical Manifestations

Without widespread vaccination, mumps is a common acute disease of children and young adults that is characterized by a nonpurulent inflammation of the salivary glands, especially the parotids. Severe manifestations may include pancreatitis, meningitis and encephalitis with hearing loss or deafness at any age and orchitis or oophoritis in young adults. Most disease manifestations are benign and self-limiting. Both symptomatic and asymptomatic mumps virus **infections** usually induce lifelong immunity. Rarely, reinfections with wild-type virus leading to typical mumps may occur.

Structure

Mumps virus shares many structural properties with the other paramyxoviruses.

Classification and Antigenic Type

Mumps virus belongs to the genus *Paramyxovirus* and exhibits most characteristics of the **Paramyxoviridae**. It occurs only in a single serotype and shares minor common envelope antigens with other *Paramyxovirus* species. The nucleotid-sequence homology between various mumps virus isolates is 90 to 99 percent.

Multiplication

Like other paramyxoviruses, mumps virus initiates infection by attachment of the HN protein to sialic acid on the cell-surface glycolipids and works together with the F protein to promote fusion with the plasma membrane. Following uncoating, the negative-sense viral RNA is transcribed by the RNA-dependent RNA polymerase to mRNAs followed by the synthesis of viral proteins which are essential for the continuation of the replication process. After assembly of the nucleocapsids (RNA, N, L, and P protein) in the cytoplasm, the maturation of the virus is completed by budding.

Pathogenesis

Mumps virus causes a systemic generalized infection that is spread by viremia with involvement of glandular and nervous tissues as target organs (Fig. 59-3). The infecting virus probably enters the body through the pharynx or the conjunctiva. Local multiplication of the virus in epithelial cells at the portal of entry and a primary viremia precede a secondary viremia, lasting 2 to 3 days. The incubation period usually is 18 to 21 days, but may extend from 12 to 35 days. Recognizable symptoms do not appear in 35 percent of infected individuals. The virus is carried to the main target organs (various salivary glands, testes, ovaries, pancreas, and brain). Viral replication takes place in the ductal cells of the glands. It is not known how the virus spreads to the central nervous system. Studies in experimental animals suggest that indirect spread occurs by passage of infected mononuclear cells across the epithelium of the plexus to the epithelial cells of the plexus choroideus. Alternatively, direct spread of virus is possible.

Shedding of the virus in salivary gland secretions begins about 6 days before onset of symptoms and continues for another 5 days, even though local secretory IgA and humoral antibodies become detectable during that time. Shedding occurs also in conjunctival secretions and urine. During the first 2 days of illness, the virus may be recovered from blood. In cases of meningitis or early-onset encephalitis, virus can be detected in cerebrospinal fluid and cells during the first 6 days after onset of disease. The virus may persist in tissues for 2 to 3 weeks after the acute stage, despite the presence of circulating antibodies. The main pathogenic changes induced by mumps virus infection in the salivary glands and the pancreas are inflammatory reactions. When the testes are involved, swelling, interstitial hemorrhage, and focal infarcts (leading to atrophy of the germinal epithelium) may occur. Infection of the pancreas disturbs endocrine and exocrine functions, leading to diabetic manifestations and increased serum amylase levels. Mumps virus infection of the pancreas has been reported to be a triggering mechanism for onset of juvenile insulin-dependent diabetes mellitus (IDDM); however, a causal relationship has not been established.

The pathologic reaction to mumps virus infection of brain tissues is generally an aseptic meningitis. Less often, the infection involves the brain neurons (as in early-onset mumps encephalitis). Histopathologic findings are widespread and include neuronolysis and ependymitis, which may lead to deafness and obstructive hydrocephalus in children. One human case of chronic central nervous system mumps virus infection has been described. The late-onset (postinfectious) type of mumps encephalitis is attributed to autoimmune reactions. Histopathologic findings are characterized by perivascular accumulation of mononuclear leukocytes, demyelinization, and overgrowth of glial cells, with relative sparing of the neurons. These findings resemble those seen in postinfectious measles, rubella, and varicella encephalitis.

The most characteristic clinical feature of mumps virus infection is the edematous, painful enlargement of one or both of the parotid glands. Commonly, the submandibular salivary glands are involved and, less frequently, the sublingual glands. Pancreatitis is uncommon as a severe illness. Epididymo-orchitis develops in 23 percent of infected postpubertal males and may lead to atrophy of the affected testicles, although rarely to total sterility. Oophoritis develops in 5 percent of infected postpubertal women. Mumps meningitis occurs in up to 10 percent of patients with or without parotitis. Encephalitis has been reported to occur in 1 in 400 cases of mumps. Transient high frequency deafness is the most common complication (4 percent), and permanent unilateral deafness occurs infrequently (0.005 percent). Primary mumps virus infection in early pregnancy may lead to abortion, but there is no convincing evidence of an increased risk of congenital defects in humans.

Host Defenses

Mumps virus infection is followed rapidly by interferon production and then by specific cellular and humoral immune responses. Interferon limits virus spread and multiplication, and its production ceases as virus levels decrease and humoral antibodies and cell-mediated immunity appear. Little is known about cell-mediated immunity to mumps virus; in contrast, the humoral antibody response is well understood.

IgM class-specific antibodies to mumps antigens develop rapidly within the first 3 days after onset of symptoms and persist for approximately 2 to 3 months. The IgG antibodies appear a few days later and persist for life. Circulating antibodies are responsible for the lifelong protection against recurrent disease, but reinfection may occur. **Parainfluenza** virus **infections**, particularly with type 3 virus, cause a rise of mumps antibody titers, contributing to the lifelong stability of the mumps antibody. Protective mumps antibody of the IgG class is transplacentally transferred to the newborn and persists in declining titers during the first 6 months of life.

Epidemiology

Mumps occurs worldwide. In urban areas the infection is endemic with a peak incidence between January and May. Local outbreaks are common wherever large numbers of children and young adults are concentrated (institutions, boarding schools, and military camps). Epidemics occur every 2 to 3 years. In rural areas, mumps tends to die out until enough susceptible individuals have accumulated and the virus is reintroduced which may lead to large outbreaks. Humans are the only known hosts.

Infection is transmitted by salivary gland secretions, mainly just before and shortly after clinical onset. In asymptomatic **infections**, peak contagion occurs within a similar period. Mumps virus is transmitted usually by direct

and close person-to-person contact and less often by the airborne route. School children (6 to 14 years old) are the main source of spread. Mumps infection is acquired later in childhood than are other paramyxovirus **infections**; 95 percent of individuals have antibody by age 15. As already mentioned, 35 percent of these **infections** are subclinical. In remote areas, a much lower percentage of children may be infected.

Active vaccination in the United States has reduced the incidence of reported mumps and mumps complications by more than 90 percent.

Diagnosis

Typical cases of mumps involving the salivary glands can usually be diagnosed without laboratory tests. An etiologic diagnosis of other clinical manifestations without parotitis (e.g., meningitis, encephalitis, orchitis, and oophoritis) requires laboratory confirmation. Acute **infections** can be diagnosed by isolating the virus from saliva, cerebrospinal fluid or urine in cell culture. Serologic evidence of acute infection is obtained e.g. with the ELISA or an immunofluorescence test early after onset of symptoms by demonstrating IgM antibodies in the first serum and later by detecting a significant IgG antibody rise in paired sera. Reinfection after previous vaccination is recognized by high titers of mumps-specific IgG antibody, mostly in the absence of specific IgM. An alternative to antibody detection in serum is the detection of IgM and IgA antibody in saliva which in the acute phase of mumps compares satisfactorily with IgM antibody detection in serum.

Control

In view of the long period of virus shedding and the 35 percent rate of subclinical infection, isolating patients with typical symptoms does little to prevent spread. Passive prophylaxis with mumps immunoglobulin prior to viremia is used for individuals at high risk, such as children with underlying disease, those in hospital wards, postpubertal males, and pregnant women. With the enzyme-linked immunosorbent assay (EIA), the immune status can be assessed in 3 hours so that immunoglobulin is given only to exposed seronegative (susceptible) individuals.

Active immunization against mumps is recommended for all children at 12 to 18 months of age in many countries. A combined live virus vaccine is available for mumps, measles, and rubella (MMR). The mumps component contains attenuated virus grown in chick embryo tissue culture. The vaccine containing Jeryl Lynn strain is well tolerated and safe in contrast to another strain (Urabe Am9). Usually it is effective only when maternal antibodies are absent. The seroconversion rate with the Jeryl Lynn vaccine strain used in the USA is >90 percent. The vaccine-induced antibody titers are lower than those following natural infection. This antibody protects generally against clinical disease but not against reinfection. Long-term vaccine-induced immunity seems to be maintained by inapparent (and sometimes also by apparent) reinfection with mumps wild-type virus and **infections** with other **parainfluenza** viruses. In spite of this, antibody may decline to very low or undetectable levels.

Mumps vaccination (two doses) has been responsible, e.g. in the USA for a 95 percent decrease in the annual incidence of reported mumps and mumps complications. To close vaccination gaps and to enhance antibody levels in previous vaccinees, a second dose of vaccine is recommended either at 6 or 12 to 13 years of age.

Measles Virus

Clinical Manifestations

Measles virus usually causes, in the nonvaccinated population, an acute childhood disease characterized by coryza, conjunctivitis, fever, and rash. The disease usually is benign but can be dangerous, causing pneumonia and acute encephalitis. In immunocompromised patients, giant-cell pneumonia and measles inclusion body encephalitis (MIBE) may occur. Defective measles virus may persist in the central nervous system after natural infection and may later cause subacute sclerosing panencephalitis (SSPE). The live vaccine has dramatically reduced the incidence of disease in developed countries, but measles still remains a major health problem in developing countries causing the death of 1.5 million children per year.

Structure

Measles virus has the structure of the family **Paramyxoviridae**, consisting of spherical, enveloped particles with a central helical nucleocapsid. The diameter of the pleomorphic particles varies between 120 and 250 nm. The nucleocapsid contains a monopartite, single-stranded, negative-sense RNA genome (molecular weight 7×10^6). It is surrounded by the nucleocapsid protein N and associated with the enzymatically active phosphoprotein P and the large protein L, both of which are involved in viral transcription and replication. The P gene also gives rise to nonstructural proteins C and V. The bilayered lipid envelope is partly of cellular origin with the matrix protein M inside and bears a fringe of spike-like projections containing the hemagglutination (H) and the hemolytic and cell fusion (F) activities.

Virion infectivity is lost readily when the envelope is disrupted spontaneously and when the virus is treated with lipid solvents.

Classification and Antigenic Type

Measles virus is a member of the genus *Morbillivirus* (Table 59-1). It differs from other paramyxoviruses in lacking neuraminidase and in having hemagglutination activity restricted to monkey and some human red blood cells. Measles virus and the other *morbilliviruses* occur only as one cross-reactive antigenic type. The natural disease is limited to humans and monkeys.

Multiplication

Measles virus multiplies like the other members of the family **Paramyxoviridae**. Attachment of particles to the cell surface is followed by fusion of the virus envelope and the cytoplasmic membranes and penetration of the nucleocapsid structures into the cytoplasm. The negative-sense RNA is transcribed by the nucleocapsid-associated enzymatically active P and L proteins. The order of genes in terms of their products is N, P, M, F, H and L. The virion RNA serves not only as a template for production of mRNA, but also for replication of intact RNA via a positive-stranded intermediate. After accumulation of genomic RNA and the different structural proteins in the cell cytoplasm, maturation takes place by budding of the virus from the cell. The cell membrane is modified by attachment of N-linked carbohydrate chains of cellular origin before virus transmembranous proteins appear at the cell surface.

The release of viral particles from single cells varies from a few hours, if the cells succumbs rapidly to cytopathology, to an unlimited time in chronic, steady-state **infections**. Development of chronic infection and diseases in the central nervous system (CNS), such as in subacute sclerosing panencephalitis may be caused by a variety of mutations. These result in a lack of viral budding, reduced expression of the viral envelope proteins, and spread of ribonucleoprotein (RNP) through the CNS in spite of massive immune response.

Pathogenesis

Measles virus causes a systemic infection, disseminated by viremia, with acute disease manifestations involving the lymphatic and respiratory systems, the skin, and sometimes the brain (Fig. 59-4). Inapparent **infections** are rare. Measles virus may persist silently for years (with constant replication of the ribonucleoprotein at very low levels) and occasionally causes subacute sclerosing panencephalitis (SSPE) and autoimmune chronic hepatitis. In immunocompromised patients, measles inclusion body encephalitis (MIBE) may occur after a shorter persistence.

Measles virus enters the host through the oropharynx and possibly through the conjunctiva. Local virus multiplication in the respiratory tract and the regional lymph nodes is followed by primary viremia with virus spread to the rest of the reticuloendothelial system, where extensive replication takes place. A second viremia, which occurs 5 to 7 days later, disseminates virus to the mucosa of the respiratory, gastrointestinal, and urinary tracts, to the skin, and to the central nervous system. In these organs the virus replicates in epithelial cells, endothelial cells, and in monocytes and macrophages. With development of serum antibodies, free virus is quickly cleared from the blood and body fluids, but virus persists for various periods in lymphoid, lung, bladder tissue, and in polymorphonuclear leucocytes.

The main pathologic change attributable to viral replication in the main target organs is an inflammatory response. Virus-infected cells contain virus antigens and inclusions in the cytoplasm and nuclei. Infected cells may fuse to form giant cells. The pathology and pathogenesis of postinfectious (allergic) measles encephalitis are the same as those of other exanthematous viral diseases.

In subacute sclerosing panencephalitis patients, mainly noninfectious viral ribonucleoprotein (RNP) inclusion bodies occur in different cell types in the gray and white matter with a strong inflammatory response and some demyelination. RNA can be detected in brain biopsies.

The temporary loss of delayed skin hypersensitivity during acute measles may be due to virus multiplication in T and B lymphocytes. The maculopapular rash is a consequence of the interaction between virus-infected endothelial cells and immune T cells. The simultaneous onset of rash and appearance of serum antibodies suggests an antibody-dependent cellular cytotoxic cause of the exanthem. In cases of dysfunction of T cells, no rash is seen and relentless progression of the infection may lead to giant-cell pneumonia with fatal outcome. Abnormal encephalograms are common during measles, suggesting frequent viral invasion of the brain.

Clinically, measles is characterized by upper respiratory tract symptoms during the prodromal stage and by the maculopapular rash during the eruptive phase. After an incubation period of 9 to 12 days, the prodromal stage starts with malaise, fever, coryza, cough, and conjunctivitis. At the end of this stage, the pathognomonic Koplik spots (red spots with bluish-white specks in their centers) appear in the oral mucosa opposite the second molars. The rash appears 1 or 2 days later, first on the head and then spreading down the body and limbs, including the palms and soles. Initially it is erythematous and maculopapular and later becomes confluent. Uncomplicated illness lasts 7 to 10 days. Otitis media caused by bacterial superinfection is the most frequent complication. Primary viral or secondary bacterial pneumonia is the most common complication responsible for hospitalization and death. Purely viral complications are croup, bronchiolitis, and the fatal giant-cell pneumonia; these often occur without rash in immunocompromised children.

A severe but infrequent atypical measles syndrome consists of high fever, atypical pneumonia and an urticarial, purpuric rash that begins peripherally and spreads centripetally. This syndromeis an allergic response to measles infection in adolescents and young adults who were inadequately immunized (mainly with killed measles vaccine) in childhood.

The acute postinfectious measles encephalitis, one of the main reason for introducing measles vaccination, has a frequency of 0.1 to 0.2 percent with a mortality of 20 percent. Permanent neurologic sequelae occur in 20 to 40 percent of cases. Rare complications may be myocarditis, pericarditis, hepatitis, appendicitis, mesenteric lymphadenitis and ileocolitis.

Mild (modified) measles develops in children who possess low levels of maternally derived or injected antibodies. If measles infection occurs during pregnancy spontaneous abortion or stillbirth and preterm delivery may occur.

Host Defenses

Little natural resistance to measles virus infection exists. Nonspecific substances, such as interferon, appear to contribute to early limitation of virus spread. Interferon may be detected until virus-specific antibodies appear. The cell-mediated immune response is associated with recovery from primary infection and also with resistance to reinfection at the portal of entry. The humoral immune response helps to eliminate extracellular virus during primary infection and to prevent systemic spread at reinfection .

The humoral immune response occurs in the three immunoglobulin classes. Lifelong persistence of serum antibodies may be due to persistence of viral antigen. Maternal IgG antibodies completely protect the infant for 6 months; between 6 and 12 months of age, subclinical infection or modified disease may occur.

In patients with subacute sclerosing panencephalitis, strikingly high titers of measles oligoclonal antibody (IgG) are present in serum and cerebrospinal fluid. Antibodies are directed against the viral proteins.

Epidemiology

In the pre-vaccine era measles occurred throughout the world, in all races and all climates, with humans as the only host. The main factors accounting for the epidemiological pattern are universal susceptibility to infection in the absence of antibody, extreme contagiousness, population density, and standard of living.

Sporadic cases occur throughout the year, with peak incidence in the late winter and early summer months. Epidemics

occur every 2 to 4 years in developed urban areas with a nonimmunized population and every 4 to 8 years in rural areas, when the number of susceptible persons reaches about 40 percent of the population. The epidemics last 3 to 4 months, until the number of susceptible persons falls below 20 percent. Local outbreaks occur in crowded institutional settings, even when less than 2 percent of the population is susceptible.

The source of infection is the virus-containing respiratory tract secretions, either airborne or transmitted by fomites. The contagious period lasts about 6 days, beginning with the prodromal symptoms and persisting until about 2 days after rash develops, at which time antibodies first appear.

In developed societies, measles infects children between 4 and 7 years of age. In underdeveloped societies, measles occurs before age 4. By age 7 to 12 years, in all but the most isolated areas, nearly all children have had measles and possess specific antibodies. In countries such as the United States, in which vaccine is used extensively, the incidence of reported disease and its complications have dropped more than 95 percent. As a result of this decreased transmission, a transitory shift to older teenagers has occurred. The incidence of measles encephalitis is almost twice as great in teenagers as in younger children. Subacute sclerosing panencephalitis follows natural measles at an estimated rate of 6 to 20 cases for every 10^6 children developing measles.

The risk of subacute sclerosing panencephalitis from live measles vaccine is 1/10 of that of natural infection. Most recent studies suggest a perinatal and early postnatal measles virus infection or vaccination as a presumable cause of Crohn's disease.

Diagnosis

Clinical diagnosis of measles is easy when the characteristic symptomatology is present. Laboratory diagnosis is indicated in cases with uncharacteristic exanthems, atypical measles, pneumonia, or encephalitis after a rash, as well as in suspected cases of giant-cell pneumonia, measles inclusion body encephalitis (MIBE) and of subacute sclerosing panencephalitis. It may also be indicated in previously vaccinated persons who show symptoms and signs of measles.

Laboratory diagnosis of acute measles can be made until about 2 days after onset of rash by demonstrating multinucleated giant cells or fluorescent antibody-staining cells in nasal secretions, urine, and skin biopsies. Isolation of measles virus is difficult and therefore not suitable for routine diagnosis. The detection of RNA by polymerase chain reaction (Rt-PCR) can also be used in complications and unusual manifestations of measles.

Routinely, measles infection is diagnosed serologically by demonstration of IgM antibodies in the first serum sample, taken 2 to 3 days after onset of rash. Rising IgG antibodies are detectable in the 2nd serum within 5 to 8 days. The antibody index (between CSF and serum titer values) when >3 is indicative of intrathecal antibody synthesis, thereby implying intrathecal viral antigens. In surveillance studies, saliva specimens can be tested instead of serum for the presence of IgM antibodies.

A serologic diagnosis of subacute sclerosing panencephalitis can be made by demonstrating extremely high IgG antibody levels without IgM in serum and cerebrospinal fluid. Such extremely high IgG antibodies without IgM are also diagnostic for the atypical measles syndrome.

Control

Quarantine is futile, because by the time the rash signals the disease, shedding has been in progress for 2 or 3 days. Passive prophylaxis with measles immunoglobulin is recommended for exposed, susceptible individuals, especially those at high risk (e.g., patients with cancer, immunosuppressed and immunodeficient patients, infants younger than 1 year of age, and pregnant women). To completely prevent measles infection, viremia must be prevented by an appropriate dose of immunoglobulin given within 3 days of exposure. Administration of immunoglobulin between days 5 and 9 after exposure cannot prevent the secondary viremia, but will modify the disease and allow immunity to develop. Disease also can be modified within 3 days of exposure by reducing the dose of immunoglobulin. Immunoglobulin may protect recipients for about 4 weeks.

Active immunization with the combined measles-mumps-rubella live-virus vaccine is recommended for all healthy 12 to 18-month-old children. Vaccine-induced antibody develops in about 94 percent of the seronegative recipients and usually persists in declining titers for more than 18 years. Natural exposure to virus may cause an antibody booster

response. Revaccination is recommended in some countries at the age of 6 and in others at the age of 12 years to reach primary vaccine failures (6-7 percent) and to boost low levels of antibody. Vaccination is also emphasized in the USA for adolescents entering college. Furthermore, live-virus vaccine should be given to anyone who does not have a history of measles or has not received live virus vaccine after the age of 15 months.

Efforts are being made for elimination of indigenous measles in the USA using strategies successful in 17 Caribbean countries, in Finland and in England. The World Health Organization (WHO) lists measles as one of the pathogens to be eradicated worldwide

No specific treatment for measles, measles encephalitis, or subacute sclerosing panencephalitis is available. Management is symptomatic and supportive. Bacterial superinfection should be treated with appropriate antimicrobial agents, but prophylactic antibiotics to prevent superinfection have no known value and are contraindicated.

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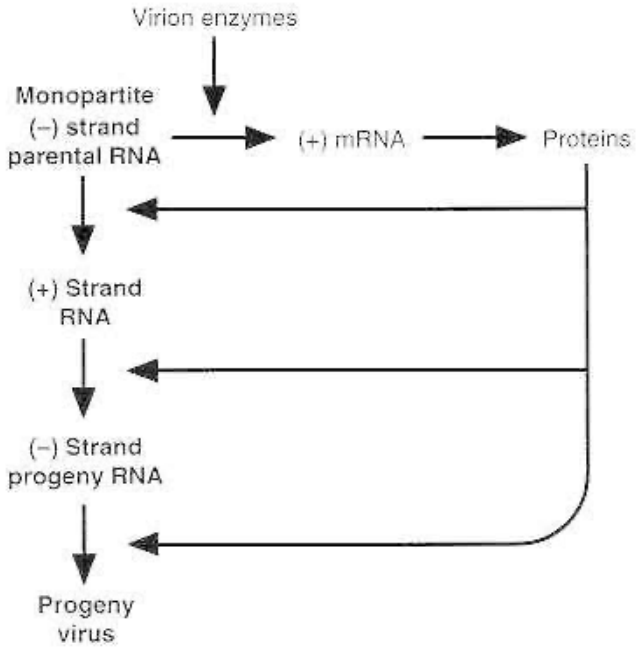
Figures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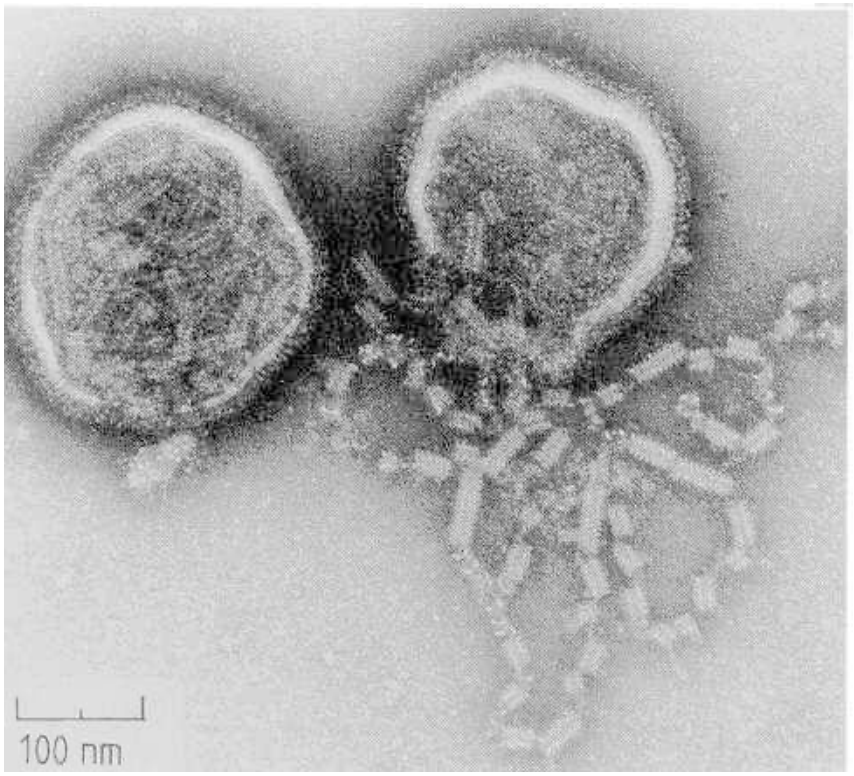

Figure 59-1 Parainfluenza virus type 1, Sendai strain

An intact virion and a disintegrating particle with free nucleocapsid fragments. (Courtesy of June Almeida, The Wellcome Research Laboratories, Beckenham, England.)

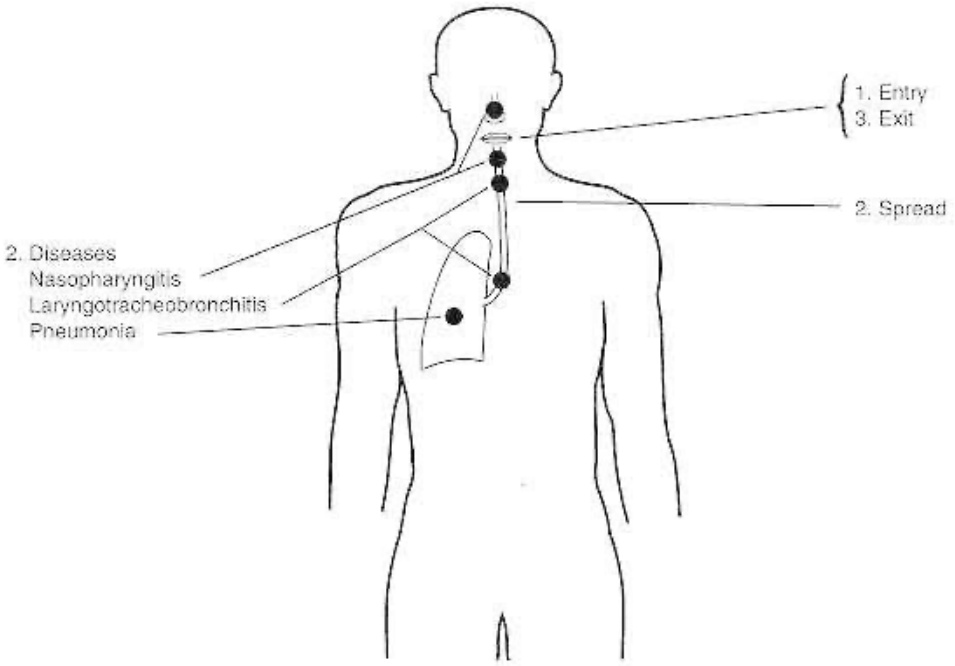

Figure 59-2 Pathogenesis of paramyxovirus and respiratory syncytial virus infections

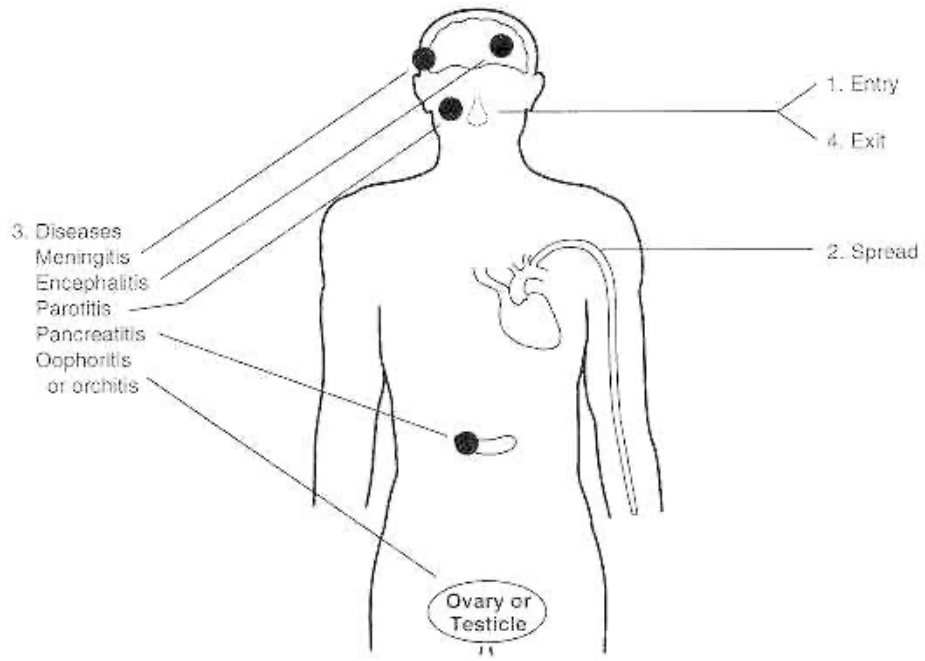

Figure 59-3 Pathogenesis of mumps virus infection

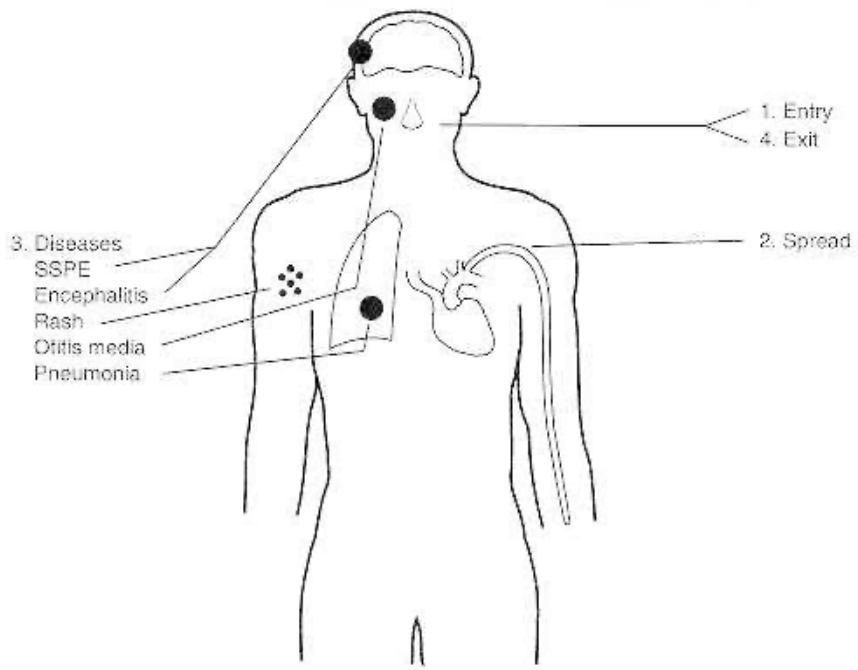

Figure 59-4 Pathogenesis of measles (rubeola) virus infection

Tables

Table 59-1 Human Paramyxoviruses

TABLE 59-1 Human Paramyxoviruses

Genus	Species	Distinguishing Properties
Paramyxovirus	Parainfluenza virus, types 1, 2, 3, 4A, and 4B, mumps virus	Contains neuraminidase and hemagglutinin; distinctive antigens
Pneumovirus	Respiratory syncytial virus	Lacks neuraminidase and hemagglutinin; morphology; distinctive antigens
Morbillivirus	Measles virus	Lacks neuraminidase; distinctive antigens

Bookshelf ID: NBK8461 PMID: 21413341