50 Paramyxoviruses

Respiratory infections; mumps; measles; Hendra/Nipah disease

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KEY POINTS

- Respiratory syncytial virus, parainfluenza viruses and human metapneumovirus are important and frequent causes of respiratory tract infections, especially in children.
- Seasonality of respiratory viruses is variable depending on the geographical region.
- Measles remains a serious disease, especially in the immunocompromised in whom it may be 'spotless' and often fatal, and in less developed countries where it contributes to significant morbidity and mortality.
- Measles is well-controlled with vaccine, but reappears quickly when the levels of herd immunity drop.
- Vaccines are available for measles and mumps viruses, but not for other paramyxoviruses.
- There are no reliable antiviral drugs for any of the paramyxoviruses other than for RSV.

The paramyxoviruses are a family of enveloped viruses containing negative sense single-stranded RNA as a single piece. They resemble the orthomyxoviruses in both morphology and their affinity for sialic acid receptors on mammalian cells, but they are larger and more fragile (Fig. 50.1A).

Within the family Paramyxoviridae there are four genera, each with several members that cause disease in man or animals (Table 50.1).

STRUCTURE AND REPLICATION

Originally, these viruses were classified together because they were thought to be similar in structure and function. Neither property is constant throughout the family but there are strong similarities.

Structure

Parainfluenza, mumps, measles, NDV and simian virus 5 are indistinguishable when seen in the electron microscope (and as described below), whereas the pneumoviruses (respiratory syncytial virus and metapneumovirus) have slightly longer surface spikes and are more difficult to visualize. The helical nucleocapsids have a herring-bone or 'zipper-like' appearance (Fig. 50.1B), which is more easily recognized than the complete particle when sought using electron microscopy.

Functionally there are other differences. Parainfluenza viruses (1–4a, b), Newcastle disease virus (NDV) and mumps virus have a surface haemagglutinin and neuraminidase located on the same spike; measles virus spikes have haemagglutinin but no neuraminidase activity; while pneumoviruses have neither. In addition, measles virus has a haemolysin not possessed by the others. Respiratory syncytial (RS) virus has a large surface glycoprotein, G, which has a cell-attaching function similar to that of a haemagglutinin; other surface spikes carry fusion (F) proteins, and all envelopes have matrix (M) proteins. In all members, the RNA is complexed with protein to form the nucleocapsid.

Replication

The replication of paramyxoviruses follows a common theme. After attachment, the F protein fuses the viral envelope to the cell membrane, becoming part of it and releasing the nucleocapsid into the cell. The negative-sense genome cannot act as messenger RNA (mRNA), making it necessary for the virus to carry its own RNA-dependent RNA polymerase. This polymerase produces subgenomic-sized mRNA transcripts, which are translated to produce some of the early virus-specific polypeptides. These include a second RNA polymerase, which copies the genome into full-length positive complementary strands that are, in turn, copied back into negative strands both

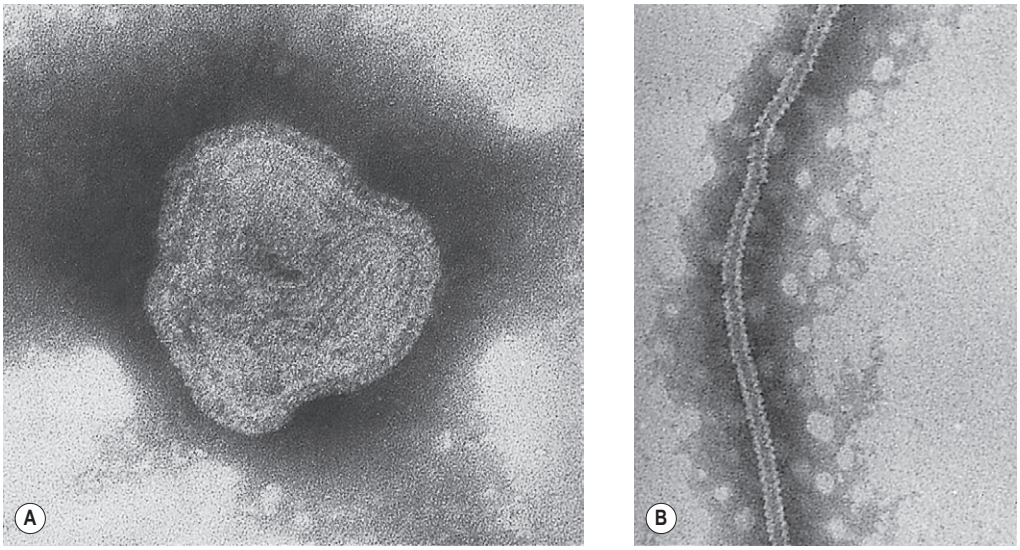

Fig. 50.1 (A) Electron micrograph of a typical paramyxovirus. (B) Separate internal helical nucleocapsid. Negative contrast, 3% potassium phosphotungstate, pH 7.0, magnification ×200 000.

Table 50.1 Classification and important pathogens of the paramyxoviruses

Genus	Human viruses	Animal viruses
Paramyxovirus	*Paramyxovirus* Parainfluenza viruses types 1, 3 *Rubulavirus* Mumps virus Parainfluenza viruses types 2, 4a, 4b	Newcastle disease virus (NDV) (poultry), simian virus 5
Morbillivirus	Measles virus	Canine distemper virus, rinderpest virus, equine morbillivirus, morbilliviruses of seals, dolphins and porpoises
Pneumovirus	Respiratory syncytial (RS) virus Human metapneumovirus (hMPV)	Turkey rhino-tracheitis virus (avian metapneumovirus)
Henipavirus	Hendra virus[a] Nipah virus[a]	Hendra virus Nipah virus

[a]These viruses cause disease in animals but can cause serious zoonotic human disease (see text).

for transcription into later mRNA (coding for structural proteins) and for incorporation into new virions. The virus haemagglutinin is incorporated into the cell membrane allowing the virus to bud off from the cell surface. Red blood cells will adsorb to the cell surface expressing the viral haemagglutinin (called haemadsorption) and this is used in the laboratory to identify virus-infected cells (see Ch. 7).

In the 1990s, two new paramyxoviruses, Hendra and Nipah, were discovered in Australia and Malaysia respectively; they are animal viruses occasionally transmitted to man. As they are genetically distinct from the other members of this family, they are classified as a separate genus. Their ecology is still being investigated and their full significance as human pathogens is not yet clear.

PARAINFLUENZA VIRUSES

CLASSIFICATION

The paramyxoviruses are subdivided into two subgenera, *Paramyxoviruses* and *Rubulaviruses* (see Table 50.1), but the distinction is not clinically relevant. There are four types of parainfluenza viruses (1–4) that are antigenically distinct. Nevertheless, there are conserved antigenic epitopes on the paramyxovirus envelope proteins, which cause the serological cross-reactions that are found between the parainfluenza viruses, mumps virus and simian virus 5. Type 4 has two subtypes, 4a and 4b, which can be distinguished only by neutralization or haemadsorption inhibition tests.

NDV is a typical paramyxovirus. It infects chickens and other domestic birds. The severity of infection varies considerably from inapparent to fatal, depending on the strain of virus. Because some strains can cause major outbreaks with high mortality, an effective live chicken vaccine based on a virulent strain has been developed. Simian virus 5 (SV5) is often present in normal uninfected monkey kidney cell cultures but does not appear to reduce their sensitivity to other viruses and does not cause human illness. Additional parainfluenza viruses are natural pathogens for cattle and other domestic species; they are not known to infect man.

CLINICAL FEATURES AND PATHOGENESIS

The parainfluenza viruses are mostly associated with:

- *croup*, a harsh brassy cough in children familiar to many parents as a middle-of-the-night irritant caused by a combination of tracheitis and laryngitis
- minor upper respiratory tract illness
- some cases of *bronchiolitis*.

They are responsible for 6–9% of respiratory infections for which a virus cause can be identified. The incubation period is 3–6 days, during which the virus spreads locally within the respiratory tract.

Many infections occur in infants in the presence of circulating maternal antibody that appears neither to be protective nor to make the illness worse.

NDV may cause a mild conjunctivitis in man, usually as a result of a laboratory accident.

LABORATORY DIAGNOSIS

Molecular methods (e.g. reverse transcription-polymerase chain reaction, RT-PCR) have been developed for detection of parainfluenza virus RNA; some of these assays have been incorporated into multiplex nucleic acid amplification tests to detect any of a number of respiratory viruses within a single reaction tube.

A rapid diagnosis may be made by immunofluorescent staining of exfoliated respiratory cells separated from well-taken nasopharyngeal secretions. There are monoclonal antibody reagents for immunofluorescent detection of parainfluenza virus types 1, 2 and 3, but reagents for type 4 are less widely available.

Similar antiviral antibodies may also be used in enzyme immuno-assays to identify viral antigen in specimens from the patient. They have the advantage of requiring only antigen to be present in the specimen, whereas other assays require intact infected cells (for immunofluorescence) or infective virus (for culture). However, enzyme immuno-assays give no information on the quality of the specimen, nor the extent of infection.

Virus may be isolated in monkey kidney cell cultures, when available. Visible cytopathic effects in the cell sheets are minimal and it is usually necessary to show infection of the cells by the haemadsorption of 1% guinea-pig or human group O red blood cells. The infecting virus can be typed (or subtyped) by coating the cell cultures with type-specific antisera before adding the red cells. Only the appropriate antibody will inhibit the haemadsorption. The typing can be confirmed by a neutralization test or by immunofluorescence.

Serology is not used routinely in diagnosis. Commonly available tests, such as complement fixation, are difficult to interpret because of cross-reactions between parainfluenza viruses and with mumps virus and, possibly, simian virus 5 as well (see above). Type-specific antibodies may be detected by neutralization or haemadsorption inhibition but these tests are too complex for routine use.

EPIDEMIOLOGY AND TRANSMISSION

In temperate regions, parainfluenza type 1 infections are more frequent in the winter, whereas type 3 is a summer infection, with small epidemics appearing reliably each year. Type 2 and 4a and 4b infections are more infrequent, in Newcastle upon Tyne at least, although elsewhere in Britain type 2 can be another

summer visitor. Type 4 infections are underdiagnosed because of a lack of suitable reagents, and reported figures are too low for epidemiological patterns to be clear. The reasons for these differing individual epidemiological patterns are unknown.

Numerically, parainfluenza infections are far fewer than those due to RS virus, and most diagnosed infections are in pre-school and primary school children. Reinfections occur but fatalities are rare. The viruses are present in respiratory secretions and are expelled during coughing and sneezing. Infection is acquired by inhalation of infected droplets and by person-to-person contact.

No vaccine is yet available for routine use.

MUMPS VIRUS

DESCRIPTION

Mumps virus is a typical paramyxovirus, indistinguishable in EM appearance from parainfluenza viruses, measles virus and NDV, with a similar ribonucleocapsid, which may be the only virus-like material seen by electron microscopy. There is only one serotype, although monoclonal antibodies have shown minor variations in the various surface antigenic epitopes.

CLINICAL FEATURES AND PATHOGENESIS

Mumps is an 'iceberg' disease which, although common as a childhood infection, is often subclinical. Although the salivary glands are often involved, inapparent or minor infections are more common. The advent of MMR (mumps, measles, rubella) vaccine as a universal vaccine of childhood has resulted in a significant age-shift, with most clinical cases in the UK now occurring in university-age adults.

Infection is probably acquired by inhalation of droplets into the respiratory tract. The incubation period is 14–18 days, and is followed by a generalized illness with later localization in the salivary glands, usually the parotids. The generalized phase is the usual 'flu-like' illness with fever and malaise, followed by developing pain in the parotid glands, which then swell rapidly. Much of the swelling is due to blockage of the efferent duct of the parotid gland, and sucking a lemon in front of a sufferer is a refined form of torture although likely to be diagnostic!

Neurological involvement is common in mumps (in more than 50% of infections), although the majority of cases are not clinically apparent. However, clinical meningitis remains the most common serious complication of mumps, occurring in 1–10% of patients with mumps parotitis. Meningitis (like any other complication of mumps) can occur before, during, after or even in the absence of salivary gland involvement. Before the widespread use of the MMR vaccine, mumps virus and the enteroviruses (see Ch. 48) accounted for most of the cases of aseptic meningitis in the UK. Mumps meningitis is rarely fatal and complete recovery is usual. Meningo-encephalitis has been described, but is much rarer, carries a poorer prognosis and may result in long-term neurological sequelae or death. Deafness and tinnitus have also been described as complications, but are very rare.

In prepubertal children the acute illness usually subsides in 4–5 days, with complete recovery. The best known complication, in postpubertal males, is *orchitis*. This, although painful and causing softening and atrophy of the affected testicle, is usually unilateral and rarely causes sterility. *Oophoritis* also occurs in girls, and should be distinguished from a ruptured ovarian cyst or acute appendicitis. Both orchitis and oophoritis usually develop as the parotitis resolves, and a history of previous parotid pain and swelling usually provides the clue.

The role of mumps in pancreatitis is difficult to establish. There may be abdominal pain in acute mumps but the levels of serum amylase do not correlate with the clinical picture. High levels may provide supportive evidence but are not diagnostic. Although uncomfortable, it is not fatal.

LABORATORY DIAGNOSIS

Detection and isolation

Typical mumps does not always require laboratory confirmation, but mild cases with little parotid swelling may not be noticed until complications develop. Demonstration of mumps virus RNA by genome amplification (e.g. RT-PCR) is the most sensitive test and should be considered for virus detection, especially in the cerebrospinal fluid (CSF) of patients with possible mumps meningitis. Isolation of the virus in cell culture (usually in monkey kidney or HEp2 cells) from throat swabs, saliva, urine or the CSF is possible, although not as sensitive as RT-PCR testing, and the virus may take up to a week to grow to detectable levels. Virus presence can be reliably confirmed by indirect immunofluorescent staining of cultured cells. Alternatively, neutralization or haemadsorption, which can be inhibited by specific antiserum,

may be used to confirm the presence and identity of the virus.

The detection of nucleocapsid helix in CSF by electron microscopy (EM) is diagnostic of mumps; however, the small quantities of CSF usually taken for all assays make routine EM diagnosis of mumps meningitis impractical.

Serology

Serological confirmation of mumps in a child is most easily accomplished by testing salivary fluid (or serum) for the presence of mumps-specific IgM. In older adults, especially those with a history of MMR vaccination, there may not be an IgM response, but high titres of IgG are strongly suggestive if the clinical picture fits. There are a number of ELISA-based and complement fixation tests available; neutralization and haemagglutination inhibition tests are more complex and do not offer any advantages in routine diagnosis.

EPIDEMIOLOGY

Mumps is a worldwide disease, with man the only known reservoir. In the absence of vaccination, most infections are in children of school age but, where MMR has been introduced, most infections occur in adults around 20–25 years of age. Infections in adults may be more severe and more likely to lead to complications. Although epidemics occur, mumps is less infectious than measles or chickenpox. Initial infection appears to confer lifelong immunity, and second infections do not occur.

CONTROL

Some, but not very reliable, protection can be given by passive immunization, which may prevent severe orchitis even when given at the stage of parotitis.

Mumps vaccine, based on the *Jeryl Lynn* or *Urabe* strains, has been available as a monovalent vaccine for some time, particularly in the USA, but is now widely incorporated into the triple MMR vaccine. All three components are live-attenuated viruses, and the mumps component induces good antibody levels, lasting long enough to suggest that the recipients will not become susceptible as adults. A few cases of mild post-vaccine meningitis have been described but have not caused serious concern.

MEASLES VIRUS

DESCRIPTION

Measles virus, a *morbillivirus*, is morphologically indistinguishable in the EM from other members of the group. The ribonucleoprotein helix is readily released from the virion and may, as with the others, be the only identifiable virus structure seen by electron microscopy. The virion structure differs from other paramyxoviruses:

- spikes carry a haemagglutinin but not a neuraminidase function
- the F protein is also a haemolysin.

There is only one serotype of measles virus and no subtypes have yet been recognized, although monoclonal antibodies show that there may be minor differences between wild and cultivated strains.

Human morbilliviruses are related to a number of animal strains. *Canine distemper* and *rinderpest* in cattle are well-known relatives, although a global campaign for the eradication of rinderpest has recently come to a successful conclusion. In the past few years other similar viruses have been isolated from seals (of several species), dolphins and porpoises, and an equine morbillivirus has reappeared that has apparently been transmitted to man in contact, fatally in one case. All are distinct and can cause serious illness in their natural species, although survivors develop solid immunity. There is partial cross-protection experimentally in ferrets between measles and canine distemper viruses.

CLINICAL FEATURES AND PATHOGENESIS

Measles is an acute febrile illness, usually in childhood, after an incubation period of 10–12 days. The onset is 'flu-like', with high fever, cough and conjunctivitis. *Koplik's spots* (red spots with a bluish-white centre on the buccal mucosa) may be present at this stage. After 1–2 days the acute symptoms decline, with the appearance of a widespread maculopapular rash. Viral antigen, but not infectious virus, may be found in the spots. The rash can be inhibited by local injections of immune serum, but does not appear at all in those who are severely immunocompromised ('spotless measles' – usually

rapidly fatal), and this has been thought to point to an immunopathological (T cell-mediated) component of the rash.

Over the next 10–14 days recovery is usually complete as the rash fades, with considerable desquamation. Complications include:

- giant cell pneumonia, more common in adults
- otitis media
- post-measles encephalitis.

The pneumonia is due to direct invasion by virus, but the role of virus in the other two complications is uncertain. Measles encephalitis can cause severe and permanent mental impairment in those it does not kill. It is rare but disastrous.

The mortality rate associated with uncomplicated measles in immunocompetent, well-nourished children is low but rises rapidly with malnourishment (particularly in Africa), in the immunocompromised and, to a much lesser extent, with age. The virus has also been devastating in isolated populations (such as the Inuit in Greenland some years ago) into which it was introduced as a 'new' disease.

One further complication of measles is *subacute sclerosing panencephalitis* (SSPE), which occurs in children or early adolescents who have had measles early in life, usually when under 2 years of age. It is a progressive and inevitably fatal degenerative disease. Within infected cells is a defective form of measles virus, which, because it is unable to induce the production of a functional M protein, is not released from the cells as complete virus. Patients deteriorate over several years, losing intellectual capacity before motor activities. Oligoclonal antibodies to measles virus proteins appear in the CSF, but the virus cannot be cultivated unless it is 'rescued' by co-cultivating neuronal cells with a susceptible cell type.

The virus has been linked with multiple sclerosis, Paget's disease of bone and Crohn's disease. In each disease, tubular structures resembling measles nucleocapsids have been seen by thin-section electron microscopy, and immunofluorescence has been used to demonstrate measles 'antigens' in biopsy material. Serum from about 50% of adults aged over 50 years, however, will fix complement with measles antigen, although the individuals give no history suggestive of recent measles, and it is possible that auto-antibodies to a measles-like protein can be induced with age. If so, its significance is unknown but must be a factor in assessing measles virus involvement in older patients with chronic diseases. The evidence linking measles virus to the aetiology of these diseases is not compelling.

LABORATORY DIAGNOSIS

The widespread use of vaccine has made the disease rarer in the community, and consequently fewer clinicians are familiar with it. There are also a number of other diseases which produce morbilliform rashes in children. Clinical diagnosis of measles therefore has a low sensitivity and specificity. Laboratory confirmation is best done by demonstration of measles-specific IgM in a venous blood or salivary sample (avoiding the need for venesection). It may also be possible to amplify the viral genome from a throat swab or other respiratory tract specimen using RT-PCR. In hospital, and particularly in immunocompromised patients in whom the disease is often rashless (and where the diagnosis may not be suspected at first), the diagnosis may be made rapidly by immunofluorescence on exfoliated respiratory cells in well-taken nasopharyngeal secretions. The presence of a large number of giant cells, particularly in patients on cytotoxic drugs, is a bad prognostic sign.

The virus may be isolated, though not readily, from blood or nasopharyngeal aspirates during the prodrome and until day 2 of rash, in human fibroblasts, primary monkey kidney cells and Vero cells. The virus can then be identified by neutralization or immunofluorescence.

EPIDEMIOLOGY

Transmission is from person to person, probably by respiratory droplets, but the associated conjunctivitis may also be a source. Measles epidemics occur every 2 years in developed countries in the absence of widespread use of the vaccine. This periodicity is absent in isolated populations too small to maintain transmission (<400 000), in poverty and overcrowding, and following the widespread use of vaccine. The disease is ubiquitous throughout the world and, although a candidate for eradication, this may be difficult to achieve due to the likely high cost and the logistic challenges such a programme poses.

In tropical areas, particularly Africa, children become infected under the age of 1 year, and the mortality rate rises in consequence, up to 42% in children under 4 years of age. Malnutrition is one of the main underlying causes of this excess mortality. The attack rate is also very high in isolated populations that have not experienced the disease for some years. In the Faroe Islands in the 1840s, three-quarters of the population were infected, although the mortality rate was low. Most of those who were not infected

were aged over 65 years, the interval since the last time the disease had been present in the islands, and confirms that infection gives prolonged immunity.

CONTROL

The first measles vaccine was a formalin-inactivated one. Although inducing circulating antibody, it was found that vaccinees exposed to natural measles were likely to develop atypical disease. The rash was more peripheral, involving the palms and soles, and pneumonia was common. It was later recognized that the vaccine had failed to induce adequate levels of antibody to the haemolytic F protein, and the immune response it induced did not inhibit cell-to-cell spread of the virus. Consequently it was withdrawn and replaced with a live-attenuated vaccine, containing the *Edmonston B* or *Schwarz* strains, which have given a seroconversion rate of over 90%. So far (over about 30 years) the immunity induced by the vaccine has persisted and may be lifelong.

Measles vaccine is now combined with those against mumps and rubella to form the MMR vaccine. This combination of three attenuated viruses has been shown to induce good immunity to all three. Introduced initially in the USA, it is now the preferred vaccine in the UK for administration to children aged between 12 and 18 months, with a preschool booster.

The attenuated measles vaccine, alone or in combination with mumps and rubella, has been shown to be effective and safe. Unfortunately, vaccine uptake fell in the UK due to fears over its safety, particularly as a possible cause of autism. These fears have now been shown to be unsubstantiated but measles reappeared when levels of herd immunity dropped.

Elimination of measles has been attempted in the USA; the number of cases was reduced from over 500 000 per year to about 2000 (a reduction of over 99%), but outbreaks in immigrants and high-school students have emphasized the problems of preventing cases from being imported into the country and of keeping up a high level of immunization.

Immunization in the regions of Africa with high levels of endemic measles still presents problems, however. Because many infants are infected before their first birthday, the vaccine has to be given to babies aged around 9 months to have any effect. Passively-transferred maternal antibody often interferes with the immune response to a live vaccine, and such early immunization does not always produce adequate and long-lasting immunity. A second dose at 12–13 months is then probably necessary, but adds to the cost and the logistic difficulties. Solutions to both will have to be found before progress is made towards substantial measles reduction in the developing world.

RESPIRATORY SYNCYTIAL VIRUS

DESCRIPTION

Superficially, RS virus resembles other paramyxoviruses, with a similar pleomorphic envelope studded with surface spikes that may be defined more clearly on electron microscopic images than those on the parainfluenza viruses, mumps and measles. The spikes may also be slightly longer, but neither the complete virus particles nor the nucleoprotein helix are easy to visualize in the electron microscope. However, individual particles are generally larger than other paramyxoviruses (Fig. 50.2).

RS virus is placed in a separate genus – *pneumovirus* – because of these minor physical differences and the lack of a haemagglutinin, haemolysin or neuraminidase. It has a G lipoprotein, a receptor for cell attachment (but not to red blood cells), which differs in chemical composition from the haemagglutinin/

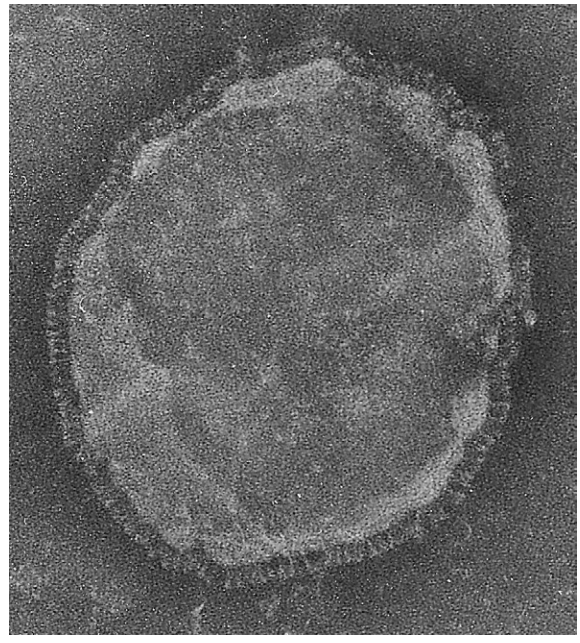

Fig. 50.2 Electron micrograph of respiratory syncytial virus. Human metapneumovirus is indistinguishable in appearance. Negative contrast, 3% potassium phosphotungstate, pH 7.0, magnification ×200 000.

neuraminidase (HN) protein of other paramyxoviruses. The F protein induces the syncytia in cell cultures from which the virus gets its name, and is probably responsible for both virus penetration and spread in the host. The virus is relatively fragile and may not survive even snap-freezing to −70°C. Specimens for isolation should therefore never be frozen.

For most purposes there is only one serotype, although the advent of monoclonal antibodies has confirmed that there are two subtypes, A and B. In Newcastle upon Tyne, strains of subgroup A have been prevalent every year since 1974, but subgroup B strains have been more erratic and have not been isolated every winter. The reason for this is unknown. Analysis of the genome has revealed further minor differences that appear to be unimportant in diagnosis (i.e. do not represent major antigenic variations) but which have allowed various strain lineages to be recognized.

RS virus is also a significant pathogen in cattle and infects chimpanzees readily – early isolates were termed *chimpanzee coryza agent*. Both goats and sheep may be infected naturally, and there is evidence that several other domestic and rodent species are susceptible, either naturally or after some adaptation.

CLINICAL FEATURES AND PATHOGENESIS

The most serious illness caused by RS virus is *bronchiolitis* in young babies, in whom the bronchiolar inflammation acts as a one-way valve leading to hyperinflation of the lungs (very characteristic on radiography), but the virus is also associated with minor upper tract infections. It usually presents with fever, wheezing, crepitations and increased transparency on chest X-ray. The peak incidence is in babies under 1 year of age. This infection is potentially life-threatening, particularly in those with bronchopulmonary dysplasia or congenital heart defects, or in those who are immunosuppressed or immunodeficient. In normal babies it is rarely fatal where medical staff have the experience and facilities for appropriate management. RS virus has been recovered from some victims of the *sudden infant death syndrome* (SIDS). Although it may have contributed to the death, other factor(s) are more significant.

While the main clinical feature is bronchiolitis, the upper respiratory tract is also infected, and this makes it possible to confirm the diagnosis with nasopharyngeal aspirates or nasopharyngeal swabs. If RS virus is present in the nasopharynx and there is clinical evidence of lower respiratory tract involvement, RS virus is likely to be responsible.

It is not uncommon for a diagnosis of 'failure to thrive' to accompany a respiratory specimen from which RSV can be recovered. Whether a failure to thrive makes the child more susceptible to the virus or whether the resultant loss of the ability to suck from the infection causes a failure to thrive is debatable but it is worth investigating such apparently unpromising specimens.

Recovery is apparently complete, although it has been suggested that the infection predisposes to chronic respiratory tract disease (e.g. asthma, bronchiectasis, etc.). This has yet to be confirmed.

The sequelae to the use of an inactivated vaccine (see below) have led to the suggestion that some of the severity of bronchiolitis is due to hypersensitivity induced by an earlier infection. Studies in various centres have neither confirmed this theory nor fully excluded it.

In older children and adults, the virus causes only minor infections, possibly because their air passages are larger. Re-infections are common due to poor RNA copying leading to antigenic drift of the immunogenic surface proteins, and in adults the virus may cause no more than a 'cold'. However, this drift emphasizes the difficulty of producing a vaccine.

There have been reports of severe illness, with some fatalities, in old people's homes as well as in the elderly living in the community. The under-recognition of RS virus in these groups may be due to the difficulty in confirming a virological diagnosis in adults and the elderly (see below).

LABORATORY DIAGNOSIS

Detection and isolation

During the acute phase of illness virus may be readily demonstrated in nasopharyngeal secretions (which are usually copious) by RT-PCR, immunofluorescence, enzyme immunoassays or culture.

Rapid diagnosis in less than 1 h with commercially available, directly conjugated, monoclonal antibodies can be made reliably by immunofluorescence, provided an adequate number of desquamated respiratory cells are collected in the secretions. Generally, similar results can be obtained with enzyme immunoassays. Such assays may be less sensitive compared with culture, but the virus grows slowly and positive results will come too late to influence management. Although antigen detection and culture methods are good for diagnosing RS virus infections in infants and young children, they are less reliable in adults and the elderly because the levels of virus or antigen are lower in adult secretions compared with those in infants,

and taking adequate specimens from adults may be difficult as the process is uncomfortable.

As with other respiratory viruses, molecular methods such as RT–PCR, either for a single virus or multiplexed to detect a panel of respiratory viruses (see under Parainfluenza viruses) can be used and may be more sensitive, especially with adult patients.

Serology

Serological assessment using complement fixation is generally not helpful. Many of the patients are too young to respond reliably and even adults do not always produce a detectable rise in serum antibody levels. However, immunoassays for the G and F proteins may be more reliable in adults where the other options are limited.

TREATMENT

Appropriate management includes use of oxygen, if indicated, and tube feeding to maintain energy intake if the baby has difficulty in suckling. Most babies can be managed symptomatically by these measures. The only specific antiviral drug available for chemotherapy is ribavirin when given as a small-particle inhalation aerosol. However its clinical efficacy remains controversial, possibly because the most affected parts of the lungs are also the least well aerated and therefore least accessible to the aerosolized drug. At present, ribavirin is only recommended for use in at-risk infants (i.e. those with lung, cardiac or immune system abnormalities) and immunocompromised patients (especially haematopoetic stem cell transplant recipients) with RSV pneumonia.

Hyperimmune RS virus immunoglobulin and humanized monoclonal antibodies have become available for the prevention and/or treatment of RS infections. These preparations are very expensive and their use may be difficult to justify except in groups at very high risk, such as very premature babies or those with pre-existing bronchopulmonary dysplasia.

EPIDEMIOLOGY

In temperate climates in both the northern and southern hemispheres, RS virus causes a substantial winter epidemic every year. In the Newcastle upon Tyne/Tyne and Wear conurbation (total population about 1 million), the annual number of virologically confirmed diagnoses regularly exceeds 500. Similar figures are obtained elsewhere where adequate facilities for diagnosis exist.

Why RS virus induces this epidemic every autumn/winter is unknown. In other regions of the world the pattern can be markedly different. In tropical regions there is an equally clear epidemic, but it occurs in the hot and humid months of the summer. Therefore, RS virus epidemics do not always correspond to the same variations in climatic factors (temperature, humidity, etc.), and sporadic cases occur anyway throughout the year. Moreover, this apparent climatic paradox is found with other respiratory viruses as well. The virus is distributed all over the world, but its activities in tropical, overcrowded and poor areas are underrecorded so far.

The significance, if any, of subtypes in explaining these RS virus phenomena is still under investigation.

CONTROL

A formalin-inactivated, crude, whole-virus vaccine was tried in the 1960s. It induced good levels of circulating antibody but failed to protect the recipients, who actually became more ill than placebo controls when subsequently exposed to RS virus. As with measles, this may have been due to the vaccine failing to induce the right protective antibodies. Subsequently, several live vaccines based on cold adaptation, temperature-sensitive mutants or administration by a different route (intramuscularly) were tried but none has yet proved satisfactory.

A major obstacle in developing a good vaccine is that the peak of disease occurs within the first year of life, and thus a safe vaccine immunogenic to such young and immunologically immature recipients is difficult to prepare. The increasing recognition that RS virus causes morbidity in the elderly may stimulate the preparation of an adult vaccine – possibly an easier challenge to meet.

HUMAN METAPNEUMOVIRUS

DESCRIPTION

Human metapneumovirus (hMPV) was discovered in the Netherlands in 2001 as an additional cause of respiratory infections, closely mimicking RSV in both the disease caused and the age-group affected. It is indistinguishable from RSV in the electron microscope (see Fig. 50.2).

It has a 13.4 kilobase genome, similar to RS virus, although slightly smaller. The order of the genes is different, resembling more closely that of an avian

virus, turkey rhinotracheitis virus. The genes, however, code for similar structural and non-structural proteins. Genetic analysis indicates that at least two separate lineages circulate world-wide; antigenic studies confirm that there may be more than one subtype (A & B), although further work is needed to clarify this.

Like RS virus, hMPV has no haemagglutinin, haemolysin and neuraminidase functions on the surface spikes. It can be cultured in tertiary monkey kidney cells, but grows slowly, and these cells are becoming less available.

CLINICAL FEATURES AND PATHOGENESIS

Clinically hMPV causes a very similar spectrum of disease to RS virus. It affects mostly young children in whom it causes a bronchiolitis with fever of up to 39°C, wheezing, crepitations, and changes on chest radiography, but all ages may be affected. There is some evidence that the virus may precipitate attacks of asthma. The proportion of respiratory patients infected with hMPV has been reported to be about 12%, and there are yearly variations in the activity of this virus.

LABORATORY DIAGNOSIS

Routine diagnosis is becoming more widely available. Molecular detection using RT-PCR is the method most often used. Culture is only possible in primary or secondary primate cell cultures which are not widely available. Although specific monoclonal antibodies are available, reliable antigen detection tests and serology are not routinely available.

TREATMENT AND CONTROL

As yet, there is no specific drug treatment, although animal models are being developed with the aim of exploring both treatment and vaccine prevention. It is likely that very similar obstacles to those found with RS virus will present the same difficulties.

EPIDEMIOLOGY

The epidemiology of hMPV is still being researched. Serological studies in the Netherlands have shown that the virus has been circulating there for more than 50 years, indicating that this is not a 'new' human virus. The seasonality of infections, where data are available, has shown similar patterns to those of other respiratory viruses, and RS virus in particular.

NIPAH AND HENDRA VIRUSES

During 1998–1999, an outbreak of respiratory disease in pigs was associated with encephalitis in humans in Malaysia. There were more than 200 human cases, with 105 deaths. The causative agent was found to be a paramyxovirus given the name Nipah. Other outbreaks of Nipah virus have been reported in India and Bangladesh without obvious involvement of pigs as an intermediate host. In some of these outbreaks there is also some evidence of limited human-to-human transmission and nosocomial infection. It is distinct genetically from all the other paramyxoviruses and most closely related to Hendra virus, another paramyxovirus discovered in 1994 causing epidemic fatal respiratory disease in horses that can be transmitted to man, resulting in fatal encephalitis. Both viruses continue to be active, with human cases occurring from time to time in Asia and Australia.

These new viruses are now officially classified as paramyxoviruses, but in a separate genus within the Paramyxoviridae. Fruit bats appear to be the natural reservoir of both viruses, with transmission to other mammals (including man) an exceptional event. Nevertheless, these discoveries underline the fact that new pathogens capable of causing human disease continue to emerge.

RECOMMENDED READING

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